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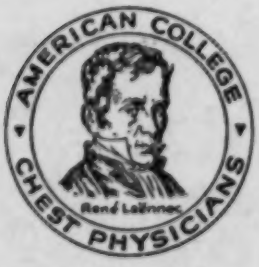
VOLUME XXVIII NUMBER 3

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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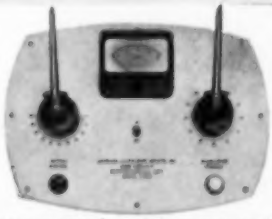

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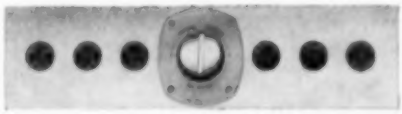

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2. Richards, D. W., Jr., Barach, A. L., and Cromwell, H. A.: Use of Vaporized Bronchodilator Solutions in Asthma and Emphysema; Continuous Inhalation Method for Severe Asthmatic States. Am. J. M. Sc., 199:225, 1940.
3. Segal, M. S.: Facts and Fancies in the Management of the Seriously Ill Patient with Bronchial Asthma. Dis. of Chest, 14:795, 1948.

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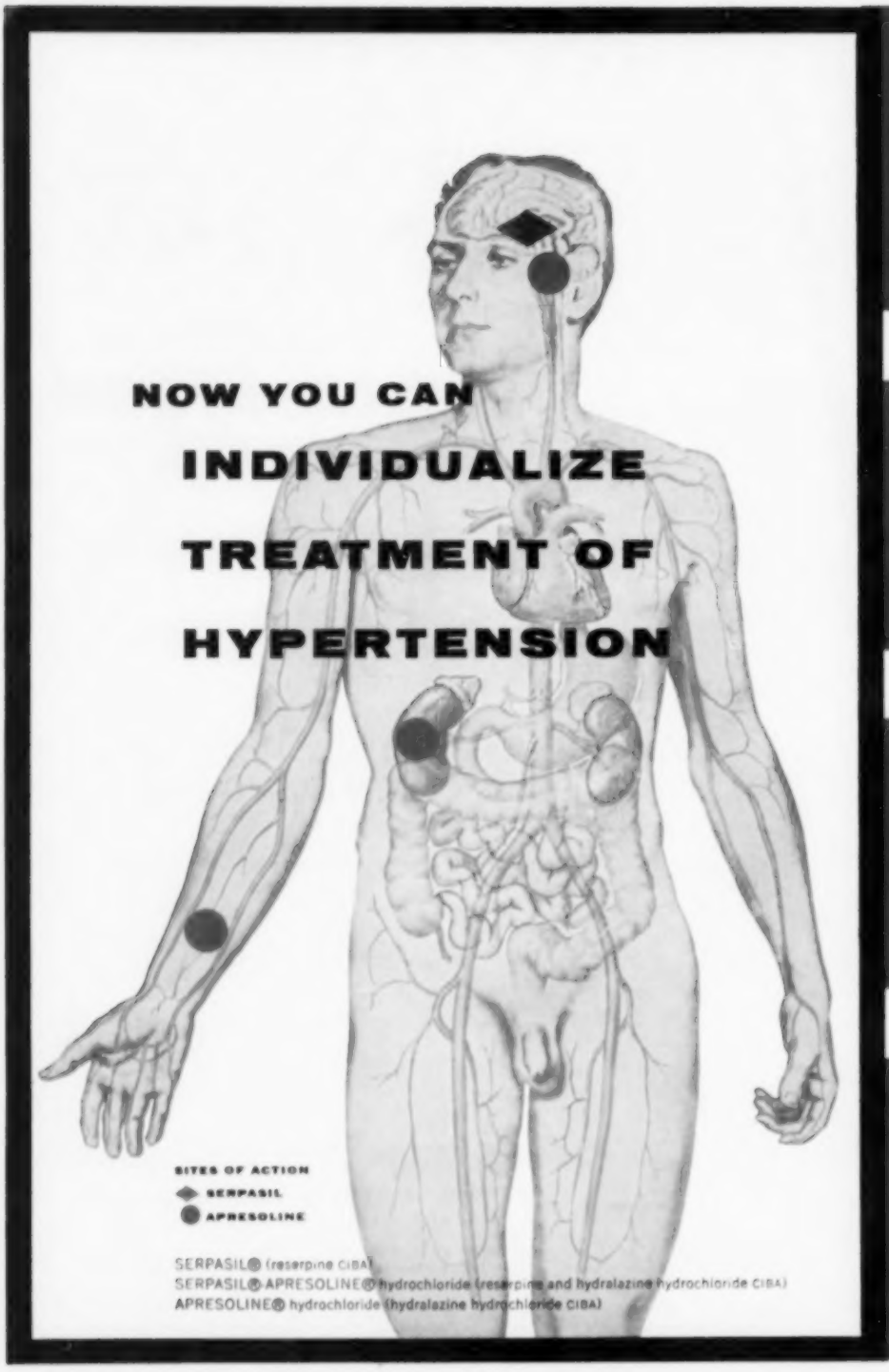
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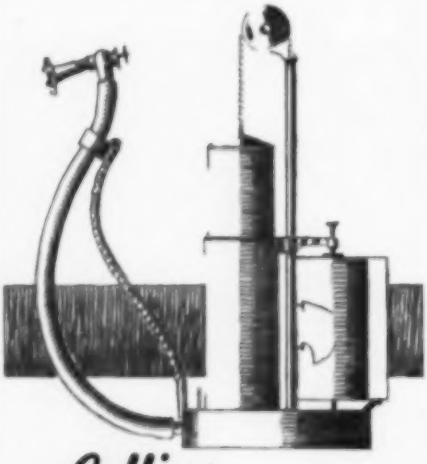

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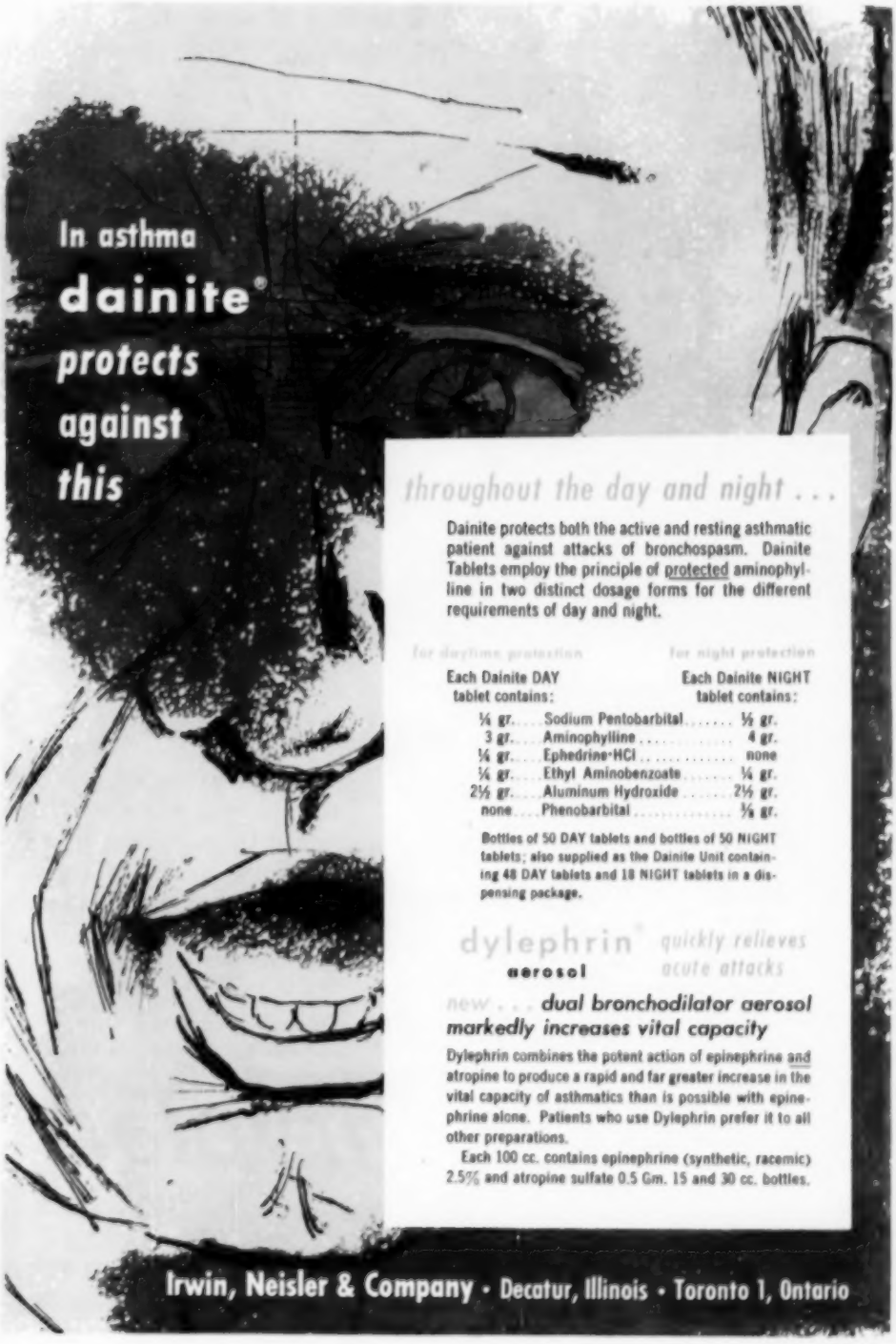

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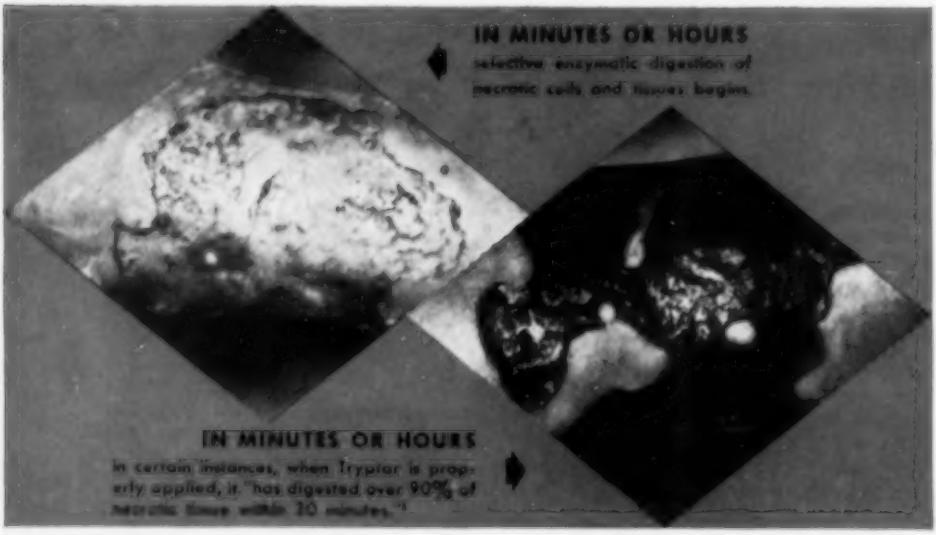
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1. Morani, A. D.: J. Am. M. Women's A. 9: 313, 1954.

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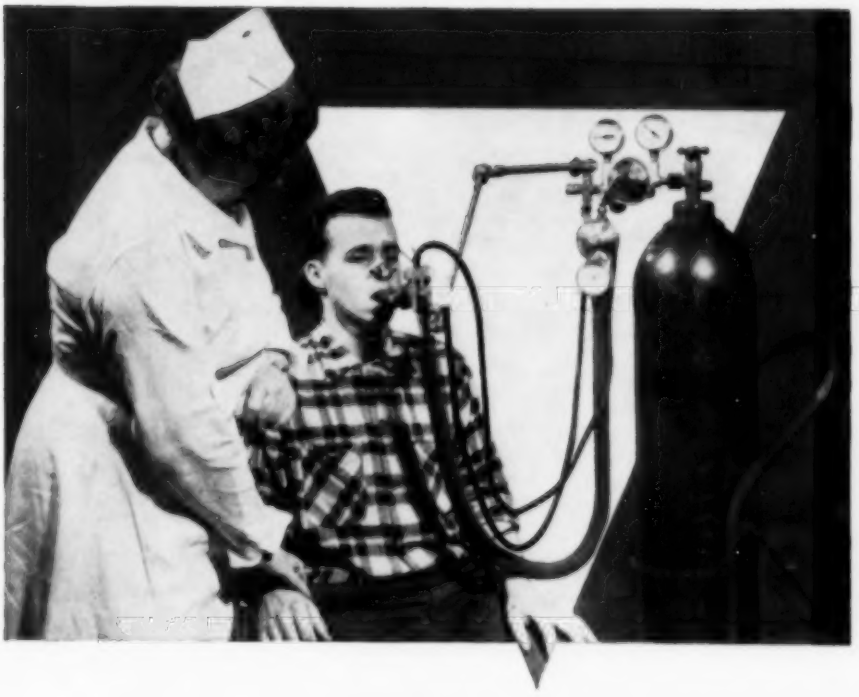

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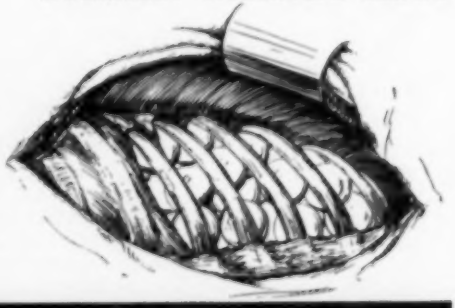

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1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

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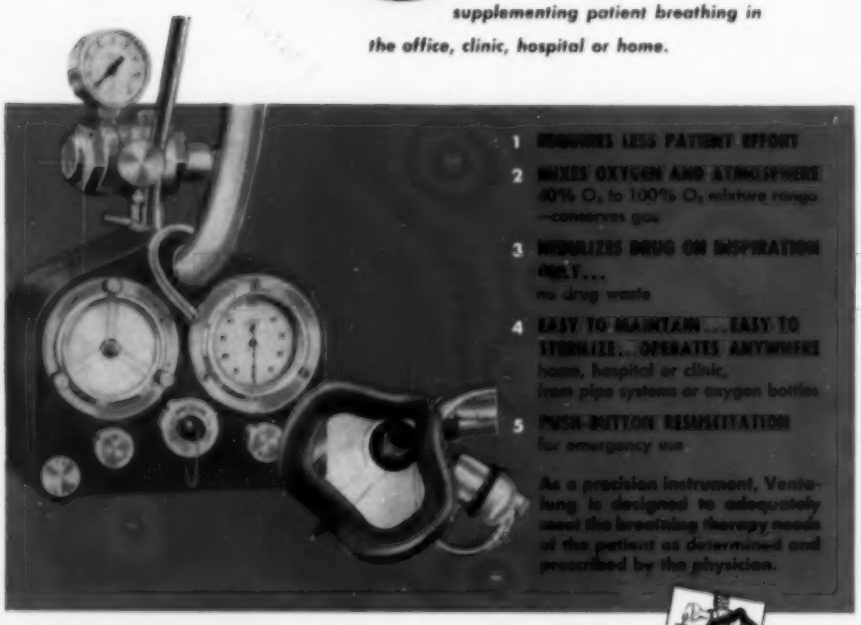
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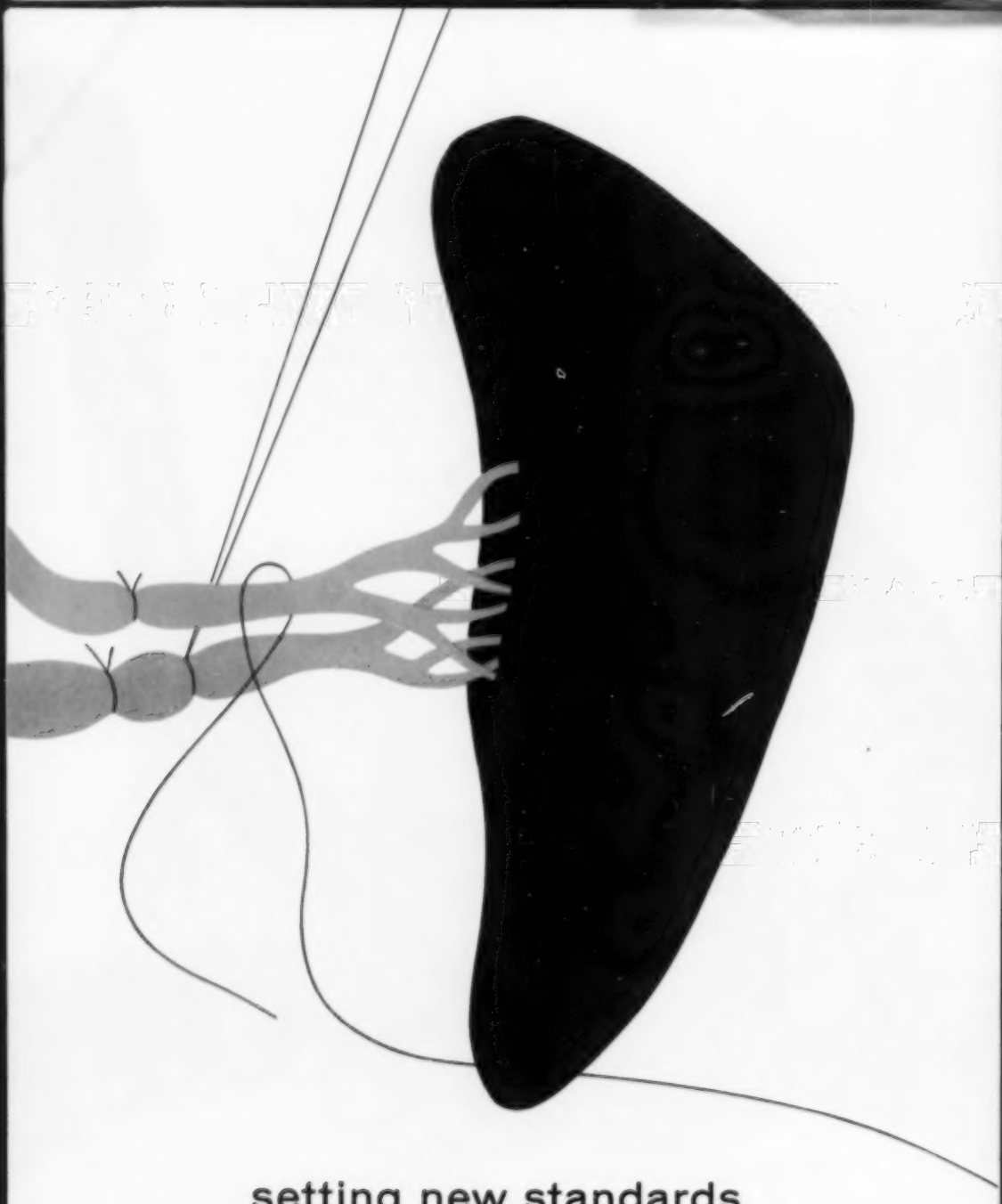

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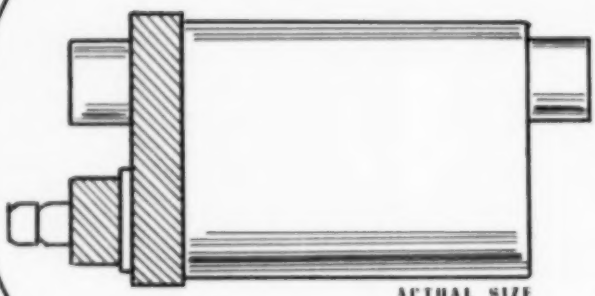

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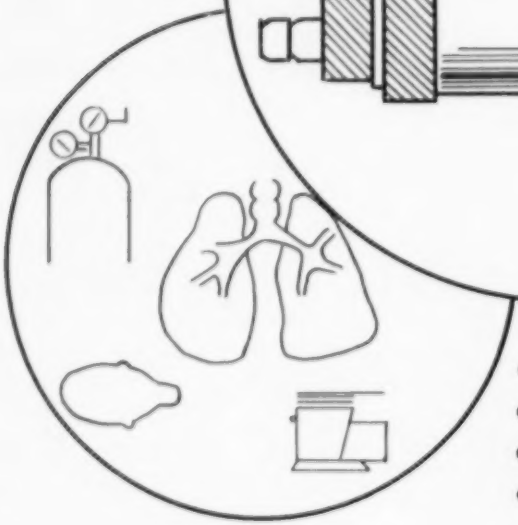

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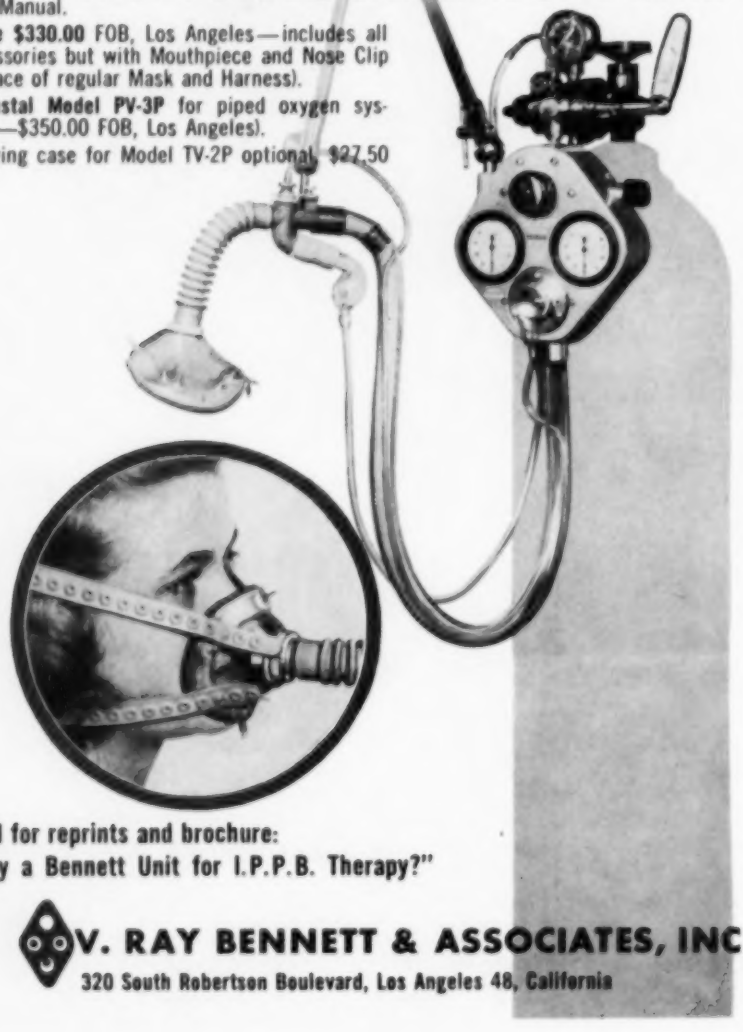

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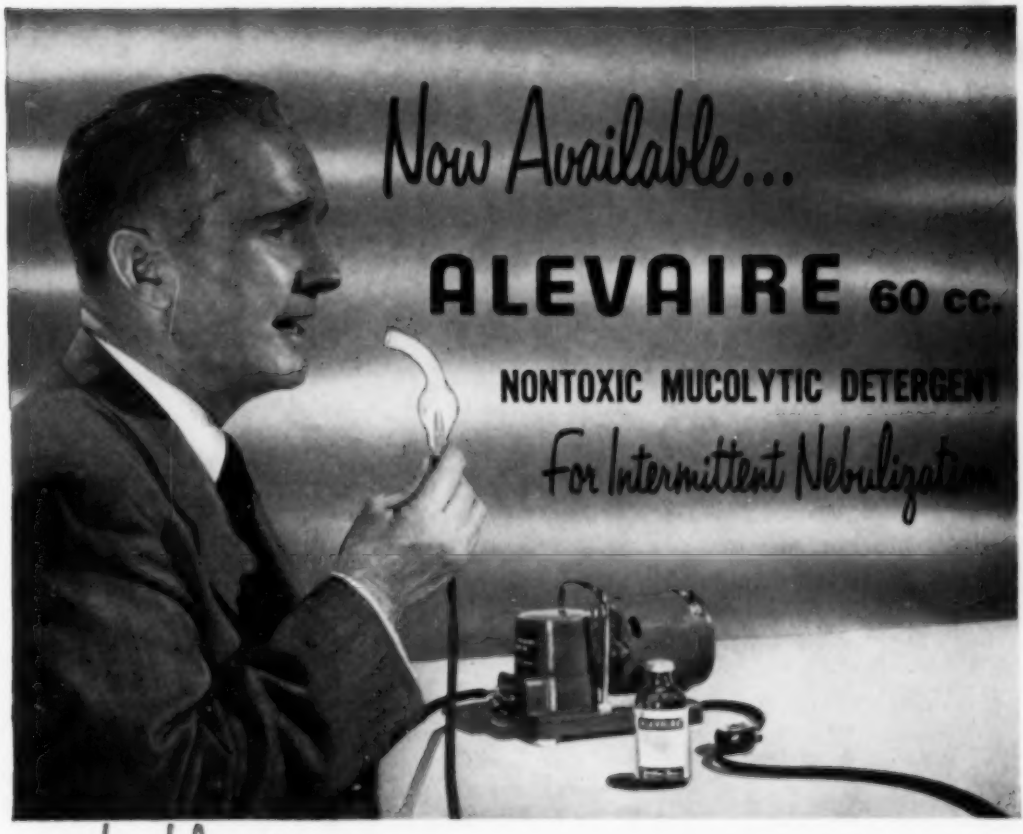

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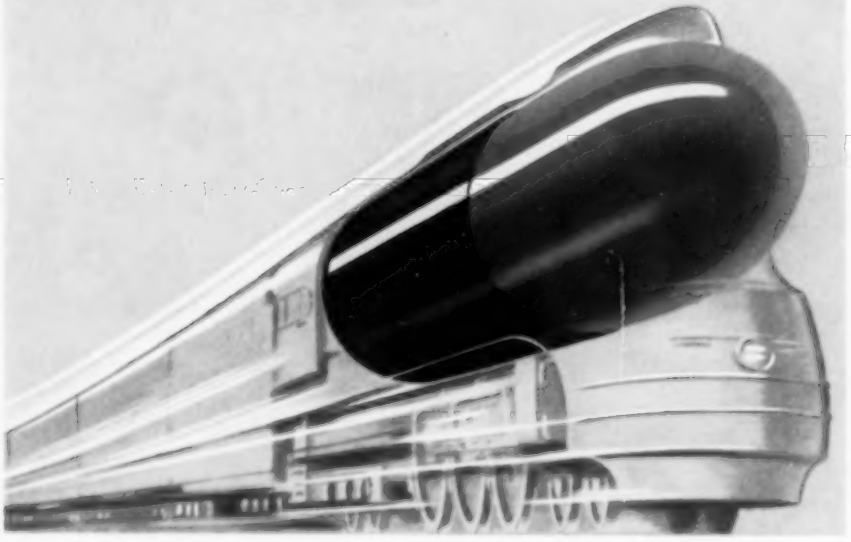

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DISEASES of the CHEST

VOLUME XXVIII SEPTEMBER, 1955 NUMBER 3

Myocarditis: A Clinical and Pathologic Study of Forty-five Cases

MISCHA J. LUSTOK, M.D., F.C.C.P., JULES CHASE, M.D. and JOSEPH M. LUBITZ, M.D.

Milwaukee, Wisconsin

I. INTRODUCTION

In recent years, pathologists, particularly Saphir,[1] have been aware of the occurrence of inflammatory changes of the myocardium in a wide variety of disease states. Clinicians, generally, have been reluctant to revive the diagnosis of myocarditis, especially in its chronic phase. In an effort to re-evaluate this type of heart involvement, a systematic screening study was undertaken of disease states in which myocarditis was frequently found in necropsy material. The bulk of the cases so studied included infections, malnutrition states, heart failure of undetermined etiology, exposure to toxins, electrolyte imbalance, and a broad group of patients whose prolonged recovery from acute illness was unexplained. Some cases, in which the diagnosis of myocarditis was first established at autopsy, were studied in retrospect.

For the purpose of clarity in presentation, cases of myocarditis occurring in conjunction with other forms of heart disease of determined etiology, such as rheumatic, hypertensive and coronary heart disease, and those associated with pericarditis, were eliminated. Only instances in which myocarditis was the primary, and, as far as could be determined, only feature of cardiac involvement, were included in this study.

TABLE 1
THE MAJORITY OF PATIENTS WERE UNDER 40 YEARS OF AGE

Age Distribution	
Under 10 years of age	1
Between 10 and 19 years	2
Between 20 and 29 years	13
Between 30 and 39 years	19
Between 40 and 49 years	5
Between 50 and 55 years	5
Total cases studied	45

From the Cardiovascular Section, Department of Internal Medicine and Department of Pathology, Marquette University School of Medicine and the Veterans Administration Hospital, Wood, Wisconsin.

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II. CLINICAL AND PATHOLOGICAL OBSERVATIONS

A total of 45 cases was studied. The age, sex and racial distribution paralleled the character of admissions to the hospitals which served as source of material. There were four females in this group. Two of the patients were Negroes (Table I).

Most of the patients gave no significant past medical history; however, in 22 of the 45 patients, chronic alcoholism was present. Concurrent illnesses occurred in 39 of the patients (Table II).

Symptoms and signs of myocarditis, in this series, are presented in Table III.

Routine laboratory studies were consistent with the changes expected during the course of the antecedent or concurrent illness. When myo-

TABLE II

THE MAJORITY OF PATIENTS PRESENTED CONCURRENT OR ANTECEDENT RESPIRATORY INFECTIONS

Concurrent Illness	
Acute upper respiratory infection	13
Virus pneumonia	9
Diphtheria	3
Bacterial pneumonia	2
Acute gastro-enteritis	2
Chronic nephritis (acute exacerbation)	2
Infectious hepatitis	2
Sarcoidosis	1
Pulmonary tuberculosis	1
Lupus erythematosus	1
Arsenic poisoning	1
Carbon monoxide poisoning	1
None	7
Total	**45**

SIGNS AND SYMPTOMS IN RELATION TO DEATHS

SYMPTOM COMPLEX	NO.	GALLOP	GALLOP AND SYST. M.	SYST M.	TICK-TACK RHYTHM	AUR. FIB.	AUR. STAND-STILL	NONE	SUD-DEN DEATH	DELAYED DEATH
SYMPTOMS OF TOTAL HEART FAILURE	24	5	4	4		1	1	9	5	4
SYMPTOMS OF LEFT HEART FAILURE	6	1			1	2		2	2	1
SYMPTOMS OF RIGHT HEART FAILURE	1			1						
OTHER (CHEST PAIN, PALPITATION, AND/OR DYSPNOEA)	10			1	2			7	1	
NONE	4	2						2		
TOTAL	45	8	4	6	3	3	1	20	8	5
GRAND TOTAL	45				45				13	

TABLE III: Heart failure was the predominant clinical syndrome.

carditis was present as a sequela of previous infection, which had run its full clinical course, laboratory evidence of infection, i.e., fever, leukocytosis, elevated sedimentation rate, was no longer present.

Electrocardiographic and roentgenologic observations are presented in Table IV and V, respectively.

Ten of the 13 patients who died during the period of observation had autopsy examinations. Pathological material from this series is summarized in tables VI-A and VI-B.

III. CLASSIFICATION OF MYOCARDITIS

Several classifications of myocarditis have been advanced. Those based on etiological considerations[2] have proved to be too unwieldy because of the multiplicity and complexity of underlying causes. No clinically acceptable classification based on pathological considerations alone has yet been offered. Some classifications based solely on the severity of the illness[3] have not taken into consideration the features of recurrence and chronicity often exhibited by this disease.

In our series, we have found that the classification below, based on the clinical course, is the most workable arrangement.

Classification of Myocarditis

I. Acute myocarditis
   A. Fulminating
   B. Benign
      1. Asymptomatic
      2. Symptomatic

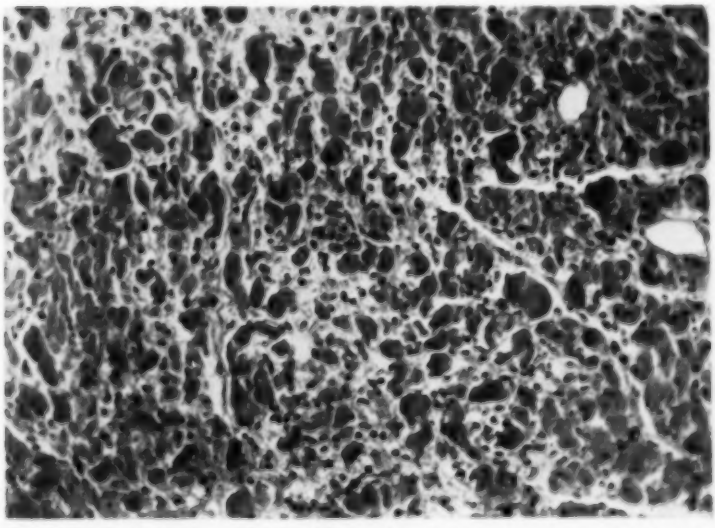

FIGURE 1 (CASE 1) C. R.: Photomicrographic (× 135). Acute fulminating myocarditis. Edema, lymphocytic infiltration and degeneration of myocardial fibers.

II. Recurrent myocarditis

III. Chronic (persistent) myocarditis

Acute fulminating myocarditis is characterized by a sudden catastrophic onset and rapid termination in death. Benign asymptomatic myocarditis is recognized by routine electrocardiographic or x-ray studies of patients ill with a disease prone to be complicated by myocarditis. In the benign symptomatic group, attention is directed to the existence of myocarditis by cardiovascular symptoms not expected in the natural course of the underlying disease, unexpected severity of illness, or prolonged convalescence. Reversibility of the myocardial involvement is a feature of this group. Recurrent myocarditis presents clinical features similar to the benign symptomatic group, except that repetition of the syndrome occurs with normal interludes. Chronic persistent myocarditis is characterized by a protracted clinical course requiring continued medicinal support or by progressive deterioration to a fatal termination (Table VII).

Correlation of this classification with etiology and past medical events was not statistically significant. However, there was a significant correlation between the clinical course and the pathological findings (Tables VI-A and VI-B).

IV. CASE PRESENTATIONS

A. Acute Fulminating Myocarditis

Eight cases fell into this group. In all instances the onset was sudden, the symptomatology overwhelming, and the course rapidly progressive toward fatal termination. In seven cases the presenting symptoms were those of heart failure. In the eighth, acute peripheral vascular collapse was present. Whenever electrocardiographic and chest x-ray examinations could be made, all cases had pronounced changes.

ELECTROCARDIOGRAPHIC CHANGES RELATED TO CLINICAL COURSE

SERIAL GRAMS	ELECTROCARDIOGRAPHIC PATTERN	NO.	TOTAL	RECOVERED	RX.	DIED
REVERSIBLE	NON-SPECIFIC T WAVE CHANGES	12		12		
	NON-SPECIFIC T WAVE CHANGES WITH FIRST DEGREE HEART BLOCK	1	13	1		
IRREVERSIBLE	NON-SPECIFIC T WAVE CHANGES	10		8	2	
	NON-SPECIFIC T WAVE CHANGES WITH LOW QRS VOLTAGE	5		2		3
	LEFT HEART STRAIN	6		1	2	3
	LEFT HEART STRAIN WITH AURICULAR FIBRILLATION	3			1	2
	RIGHT HEART STRAIN PATTERN	2			1	1
	AURICULAR STANDSTILL WITH IDIOVENTRICULAR RHYTHM	1	27			1
NORMAL		2	2	2		
NONE TAKEN		3	3			3
TOTAL		45		26	6	13

TABLE IV: The majority of the cases showed localized or generalized non-specific T-wave changes. The extent and reversibility of the electrocardiographic changes seemed to parallel the clinical course. The incidence of arrhythmias and A-V block was notably low.

Case 1. C. R. an eight year old white female was admitted to Milwaukee County Emergency Hospital on April 4, 1950, with the complaint of weakness and abdominal pain of two days' duration. Past medical history was negative. The child was acutely ill and cyanotic. The neck veins were distended. The heart was enlarged 10 cm. to the left and 7 cm. to the right of the midsternal line. The heart rate was 20 per minute with regular rhythm. Grade III systolic murmur was present at the apex. The blood pressure was 90/50. The lungs were clear. The liver extended below the umbilicus and was tender. No edema was present.

Urinalysis revealed 3 plus albumin. The white blood cell count was 23,000 per mms. The red blood cell count and hemoglobin were normal. The nonprotein nitrogen was 81 mg. per 100 ml. A blood culture was negative.

An electrocardiogram revealed auricular standstill with idioventricular rhythm.

General supportive measures were instituted. The course was progressively worse. Cheyne-Stokes respiration was followed by convulsions and death 11 hours after admission.

Autopsy examination was done (AC-179-50). The abdomen contained 100 ccs. and the right pleural cavity 250 ccs. of fluid. The lung showed pleural hemorrhages. The pericardial sac contained 30 cc. of fluid. The heart was dilated. The auricular appendages contained antemortem thrombi. The myocardium was pale, yellow-tan and soft.

X-RAY AND FLUOROSCOPIC CARDIAC FINDINGS IN RELATION TO CLINICAL COURSE

SERIAL X-RAYS*	SIZE AND CONTOUR	NO.	TOTAL	RECOVERED	RA.	DIED
REVERSIBLE	MILD-MODERATE GLOBOSE	10		10		
	SEVERE GLOBOSE	6		5	1	
	LEFT HEART MASS	1	17	1		
IRREVERSIBLE	MILD-MODERATE GLOBOSE	5		2	2	1
	SEVERE GLOBOSE	7		1		6
	LEFT HEART MASS	3		1	1	1
	RIGHT HEART MASS	1	16			1
NO CARDIAC ENLARGEMENT		8	8	6	1	1*
NO X-RAY EXAMINATION		4	4		1	3
TOTAL		45	45	26	6	13

*ACUTE FULMINATING

TABLE V: The usual cardiac contour was that of globose enlargement with reduced muscular excursions. Reversibility paralleled the clinical course.

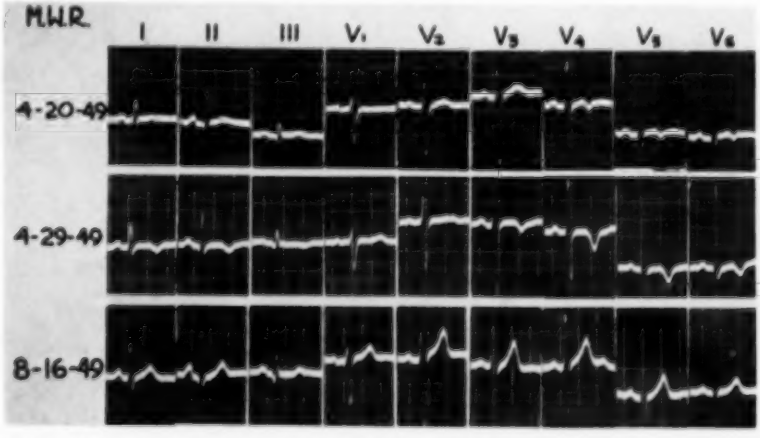

FIGURE 2 (CASE 2) M. W. R.: Acute benign symptomatic myocarditis. Progressive T-wave changes with complete reversal to normal.

Microscopically (Figure 1), the heart showed focal areas of necrosis and inflammation. The tissue was edematous with foci of lymphocytes, monocytes, polymorphonuclear cells and occasional eosinophilic cells. The leukocytic infiltration involved both interstices and parenchyma. The myocardial fibers in the areas of necrosis were swollen, granular, with loss of striation and degeneration of nuclei. The liver showed acute central necrosis.

B. Benign Asymptomatic Myocarditis

Four cases fell into this group. In all instances, there were no symptoms or signs which might have called attention to the heart. Two cases showed completely reversible electrocardiographic changes, and two did not revert during the period of observation. Normal chest x-ray films were the rule. Discovery of these cases was based on electrocardiographic findings only.

Greater numbers of this category of myocarditis have been discovered in other studies[4, 5, 6, 7] in which serial routine electrocardiograms were taken during the course of illnesses known to have a high incidence of myocardial involvement. Our method of case finding was dependent upon bedside suspicion of the presence of this clinical entity aroused by suggestive symptoms or signs.

C. Benign Symptomatic Myocarditis

This category, a total of 20 cases, represented the largest single group. While variations occurred, a basic historical pattern was evident. In the average case, against a background of alcoholism, a young adult with no previous cardiac history would develop signs or symptoms of congestive heart failure during or after a bout of seemingly ordinary respiratory infection. Less frequently, other cardio-pulmonary symptoms, such as dyspnea, chest pain or palpitation, or signs such as systolic murmur,

SUMMARY OF PATHOLOGIC FINDINGS

NAME	CLINICAL CLASSIFICATION	HT. WT.	GROSS HEART	MICRO. HEART	EVIDENCE OF HEART FAILURE	CORONARY VESSELS	CAUSE OF DEATH	OTHER CONDITIONS
				ACUTE MYOCARDITIS				
E.M.	ACUTE FULMINATING	300	RV 6 MM., LV 13 MM., FLABBY, GRAY-TAN	LYMPHOCYTIC AGGREGATES	EDEMA CONGESTION	SLIGHT ARTERIOSCLEROSIS	HEART FAILURE	
E.H.	ACUTE FULMINATING	350	RV 4-6 MM. LV 18 MM. SOFT, RED-BROWN	B.V. SLIGHTLY THICKENED. EDEMA. INCREASE OF MONOCYTES & LYMPHOCYTES	C.P.C. PULMONARY EDEMA. ANASARCA	MODERATE ARTERIOSCLEROSIS	HEART FAILURE	PULMONARY TB, NOT ENOUGH TO CAUSE DEATH
J.S.	ACUTE FULMINATING	370	RV 5 MM. LV 22 MM. DULL, PURPLE-BROWN	EDEMA. SCATTERED LYMPHOCYTES, PMN AND EOSINOPHILS	HYDROTHORAX	MODERATE ARTERIOSCLEROSIS	BILATERAL PNEUMONIA ARTERIOSCLEROSIS	ACUTE NEPHRITIS
C.R.	ACUTE FULMINATING		SEROSAL HEMORRHAGE ANTE-MORTEM CLOT IN RT. AURICLE SOFT, PALE, YELLOW-TAN	EDEMA, NECROSIS FOCI OF LYMPHOCYTES, MONOCYTES, PMN, RARE EOSINOPHILS	ASCITES HYDROTHORAX HYDROPERICARDIUM, ANASARCA, LIVER CONGESTIVE NECROSIS	NORMAL	HEART FAILURE	
M.B.	ACUTE FULMINATING		FIRM, TAN-RED	EDEMA, SCATTERED LYMPHOCYTES, RARE AREA OF PMN AND EDEMA		NORMAL	ACUTE NEPHRITIS	
A.D.	ACUTE FULMINATING	350	RV 3 MM. LV 15 MM. NORMAL CONSISTENCY RED-BROWN	EDEMA, INTERSTITIAL EOSINOPHILIC PMN AND MONOCYTIC INFILTRATION	PULMONARY EDEMA, HYDROTHORAX HYDROPERICARDIUM	NORMAL	HEART FAILURE	ADDISON'S DISEASE, SARCOIDOSIS

TABLE VI-A: Cases of clinical acute myocarditis show microscopic evidence of acute myocardial damage.

tick-tack or gallop rhythm, were present without other evidence of congestive heart failure. The electrocardiograms would show non-specific T-wave changes which later became normal on serial study. Cardiac enlargement, which was characteristically globose in contour, was present, and would return to normal by the time of clinical recovery. In a smaller group, the electrocardiographic and x-ray changes did not revert to normal, either because of too brief a period of follow-up study, or possible permanence of the myocardial damage. All of these 20 patients made com-

SUMMARY OF PATHOLOGIC FINDINGS

NAME	CLINICAL CLASSIFICATION	HT. WT.	GROSS HEART	MICROSCOPIC HEART	EVIDENCE OF HEART FAILURE	CORONARY VESSELS	CAUSE OF DEATH	OTHER CONDITIONS
				CHRONIC MYOCARDITIS				
J.D.	PERSISTENT	620	DILATED, FLABBY, ENDOCARDIAL SCAR AT APEX 2 X 1 1/2 CM RV 6 MM. LV 13 MM. BROWN-TAN	EDEMA, CONGESTION INTERSTITIAL AND FOCAL FIBROSIS, INFILTRATION OF LYMPHOCYTES, MONOCYTES, AND RARE PMN; NUCLEAR DEGENERATION	HEMORRHAGIC EDEMA OF LUNGS, ANASARCA, LIVER-CONGESTIVE NECROSIS	VERY SLIGHT ARTERIOSCLEROSIS	HEART FAILURE	
M.S.	PERSISTENT	400	SOFT INDISTINCT RV 6 MM. LV 9 MM. RED-BROWN	ENDOCARDIAL FIBROSIS, FOCAL & INTERSTITIAL FIBROSIS, EDEMA, DEGENERATION OF FIBERS, LYMPHOCYTES, FIBROBLASTS, MONOCYTIC INFILTRATION	C.P.C. EDEMA	NORMAL	HEART FAILURE	PULMONARY ARTERIOSCLEROSIS & HYPERTENSION
L.B.	PERSISTENT	630	ROUNDED, FLABBY, DILATED, MOIST RV 3 MM. LV 20 MM. RED-BROWN	DIFFUSE INTERSTITIAL FIBROSIS & GRANULATION TISSUE, FIBROUS REPLACEMENT, INTERSTITIAL EDEMA, MONOCYTES FIBROBLASTS	C.P.C. PULMONARY EDEMA, HYDROTHORAX	MILD ARTERIOSCLEROSIS	HEART FAILURE	PORTAL CIRRHOSIS
J.K.	RECURRENT, GOING TO PERSISTENT	590	ROUNDED, FLABBY, RV DILATED LV 10 MM. RT. AURICULAR THROMBUS	FOCAL SCAR, IRREGULAR NUCLEI, EDEMA	ANASARCA ASCITES HYDROTHORAX HYDROPERICARDIUM	NORMAL	HEART FAILURE	PULMONARY INFARCTIONS

TABLE VI-B: In persistent chronic myocarditis, a large heart is found with subacute and chronic myocardial changes seen microscopically.

FIGURE 3

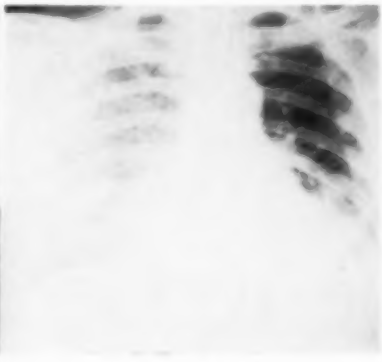

FIGURE 4

Figure 3 (CASE 2) M. W. R.: Chest x-ray two weeks prior to hospital admission.—*Figure 4* (CASE 2) M. W. R.: Progressive pulmonary and pleural changes with striking cardiac enlargement and non-specific configuration.

plete clinical recovery, and did not require subsequent maintenance medication.

While the composite clinical pattern is described above, not all of the diagnostic features were present or of equal intensity, in any one case.

Case 2. M. W. R. a 44 year old white male was admitted to the Veterans Administration Hospital, Wood, Wisconsin on April 20, 1949, with complaints of chills, fever and precordial discomfort, of three days' duration. One month previously, a similar episode was treated with antibiotics by his family physician in another city. The past medical history revealed treatment for pneumonia and pleurisy in 1941 and hemoptysis of undetermined etiology in 1947. He admitted excessive use of alcohol during the past several years.

He was pallid, ill, but not in acute distress. Temperature was 100.6° F. The heart was not enlarged to examination. The heart tones were of good quality. The second pulmonic sound was greater than the second aortic. No murmur was heard. The heart rate was 64 per minute and regular. Blood pressure was 135/86 mm. Hg. There were dullness and diminished breath sounds over the left base posteriorly. Crepitant rales were heard in this area. The remainder of the physical examination was not remarkable.

The urine was loaded with red blood cells, and showed 2 plus albumin. The hemoglobin was 10.5 grams. The red blood cell count was 3.64 million per mms. The white blood count was 12,600 per mms. with 85 per cent neutrophiles, eight lymphocytes, two monocytes and five eosinophiles. Sedimentation rate was 127 mm. in one hour (Westergren).

Admission electrocardiogram showed non-specific T-wave changes in the standard and left precordial leads (Figure 2). Chest x-ray film on the day of admission revealed diffuse clouding of the right lung and left base with minimal pleural effusion on the left (Figure 4). The cardiac silhouette was grossly enlarged and non-specific in configuration. Compared to a film taken two weeks previously (Figure 3), the change in the cardiac area and contour was striking.

He received supportive therapy and restricted activity. No antibiotics were given. The temperature returned to normal on the second hospital day and remained normal throughout the period of hospitalization. Symptoms completely cleared after several days. Serial urine studies revealed the appearance of casts in addition to the red cells present on admission, but both rapidly disappeared from the urine. The blood count and sedimentation rate slowly returned to normal levels over a period of four weeks. Blood chemistry, blood cultures and sputum cultures were normal.

Serial electrocardiograms showed progressive T-wave changes for the first 10 day period. Retrogressive changes were first noted about two weeks after admission

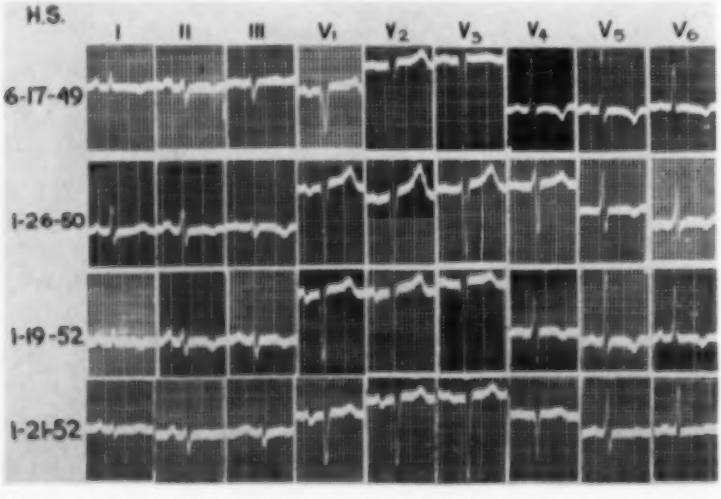

FIGURE 5 (CASE 3) H. S.: Recurrent myocarditis. Abnormal T-waves with reversal toward normal during two separate episodes of clinically active myocarditis.

and continued slowly, reaching a normal pattern at the end of four months.

Cardiac fluoroscopy on the third hospital day confirmed the degree of cardiac enlargement, globose in configuration, and demonstrated the same contour on change of position.

Chest x-ray films taken two weeks after admission showed clearing of the pulmonary lesions and marked reduction in the area of the cardiac silhouette with restitution of normal contours. Normal heart size and contour persisted through the rest of the hospital stay.

All findings reverted to normal early in the course except for the elevated sedimentation rate and electrocardiographic pattern. He reduced his physical activity until both the sedimentation rate and electrocardiogram became normal. He was discharged on September 27, 1949, without maintenance medication.

He was seen in the hospital one year later, for another condition, at which time follow-up studies failed to reveal any evidence of myocarditis.

D. Recurrent Myocarditis

There were four cases in this group. Initially, these cases were classified as benign symptomatic myocarditis, when regression of symptoms and findings occurred after the first clinical episode. After a varying but long asymptomatic period, during which no maintenance medication was required, the clinical syndrome of myocarditis recurred and serial clinical, electrocardiographic and x-ray changes were again noted. The second, and occasionally third, episode of myocarditis did not vary essentially in its manifestations from the first event. These cases were then reclassified as recurrent myocarditis.

Case 3. H. S. a 40 year old white male was admitted to the Veterans Administration Hospital, Wood, Wisconsin on June 10, 1949, with complaints of progressive dyspnea and cough. Two months prior to admission, he developed chills, fever and paroxysmal cough. Under the care of his private physician, chest x-ray films were taken and virus pneumonia was diagnosed. After two weeks of penicillin administration, the patient improved and the chest x-ray film returned to normal. Subsequently, cough recurred and effort breathlessness developed progressing to dyspnea at rest. This led to the hospital admission. The past medical history was not remarkable.

He was dyspneic and orthopneic. The temperature was normal. The heart was enlarged to the left. The heart tones were muffled, and a gallop rhythm was heard at the apex. The second pulmonic sound was louder than the second aortic sound. Pulse was 110 per minute and regular. Blood pressure was 104/82 mm. Hg. Flatness and absent breath sounds were found at the right base. The liver was not enlarged,

FIGURE 6

FIGURE 7

Figure 6 (CASE 3) H. S.: Cardiac enlargement of globose configuration and pulmonary congestive changes present on first admission.—*Figure 7* (CASE 3) H. S.: Reversal of cardiac and pulmonary changes.

and there was no ankle edema. The rest of the physical examination was non-contributory.

Routine urinalysis and blood count were normal. Sedimentation rate was 6 mm. in one hour. Kidney and liver function tests and agglutination studies were negative.

Electrocardiogram revealed T-wave inversion in the limb leads and in V-5 (Figure 5). Cardiac fluoroscopy revealed a globose enlargement of the heart with diminished muscular excursions. Pleural effusion was present on the right.

On bed rest alone he steadily improved. He lost 10 pounds in weight, and his dyspnea gradually disappeared. Serial electrocardiograms revealed regression of T-wave changes. The heart size became progressively smaller, and the muscular effort steadily improved (Figures 6 and 7). He was discharged after six weeks of hospitalization without maintenance medication.

Follow-up examination, six months later, revealed that he was asymptomatic on a full work schedule. The electrocardiogram showed further regression of the T-wave changes, and the heart was of normal size and contour.

He was well until April, 1951, an interval of 21 months, when he again noted increasing shortness of breath, and for the first time, paroxysmal nocturnal dyspnea. He was re-admitted to the hospital on June 28, 1951.

The patient was dyspneic and orthopneic. The temperature was normal. The heart was enlarged, and the heart tones were of tick-tack quality. The second pulmonic sound was accentuated. There was no murmur. Heart rate was 100 per minute and regular. The blood pressure was 102/80. There were scattered coarse inspiratory moist rales throughout both lung fields. The liver was not enlarged. There was no ankle edema. The rest of the physical examination was not remarkable.

Routine laboratory studies were normal. The initial electrocardiogram showed progression of the T-wave changes compared to tracings taken during the asymptomatic interval. The heart, previously normal in size, again showed generalized enlargement with globose contour and decrease in amplitude of contraction.

He was again treated with bed rest and supportive measures, but no specific cardiac therapy. The symptoms subsided during the first week of hospital management, but the abnormality of the electrocardiogram and cardiac silhouette regressed much more slowly. He was discharged on August 30, 1951, after two months of hospitalization, with no supportive medication, but with a recommendation to restrict his physical activity.

He was re-examined on November 14, 1951, at which time he was free of symptoms and on a full work schedule. Tick-tack rhythm was still present. The rate was 80 per minute and regular with the blood pressure of 110/80. The electrocardiogram and chest x-ray showed no significant change when compared to the studies at the time of discharge from the hospital.

About December 15, 1951, he again experienced paroxysmal nocturnal dyspnea, which progressed to orthopnea. He was re-admitted on January 19, 1952, after a five

CLASSIFICATION OF MYOCARDITIS IN RELATION TO CLINICAL COURSE

CLASSIFICATION BASED ON CLINICAL COURSE	NUMBER OF CASES	SYMPTOMS & SIGNS			ELECTRO-CARDIOGRAMS				CHEST X-RAY & FLUOROSCOPY				CLINICAL COURSE		
		HEART FAILURE	OTHER	NONE	REVERSIBLE	IRREVERSIBLE	NORMAL	NONE TAKEN	REVERSIBLE	IRREVERSIBLE	NORMAL	NONE TAKEN	RECOVERED	REQUIRES MAINTENANCE RX.	DIED
ACUTE FULMINATING	8	7	1			5		3		4	1	3			8
BENIGN ASYMPTOMATIC	4			4	2	2					3	1	2	2	
BENIGN SYMPTOMATIC	20	11	9		10	8	2		13	3	4		20		
RECURRENT	4	4			1	3			3	1			4		
CHRONIC (PERSISTENT)	9	9				9			1	8				4	5
	45	31	10	4	13	27	2	3	17	16	8	4	26	6	13

TABLE VII: The physical findings, electrocardiographic and x-ray changes, parallel the clinical course.

month asymptomatic interval. The findings were similar to those reported for the first two admissions, but greater in severity. Because of these symptoms, more intensive therapy was administered. A seven day course of terramycin was given without effect. He was then placed on a low sodium diet for one week with doubtful improvement in symptoms. After failure of above, digoxin was added, and the clinical symptoms improved. However, toxic eye signs and extrasystoles were noted with subclinical doses of digoxin, and the drug was discontinued after two weeks of administration. Mercurial diuretics were added to the management without clinical benefit. All therapy was then discontinued except for bed rest and salt restriction, and he continued slowly to approach satisfactory, but borderline, cardiovascular balance.

He reached a clinical plateau. Cardiac catheterization was done at this time. The cardiac output was 4.0 liters per minute, and the cardiac index was 2.1 liters per minute. The right auricular pressure was 2 mm. of Hg. The right ventricular pressure was 28/0 mm. of Hg. The Pulmonary artery pressures were 28/16 mm. of Hg. The mean pulmonary capillary pressure was 18 mm. of Hg., which was consistent with persistent left ventricular failure. Oxygen saturation studies revealed no evidence of intracardiac shunts.

Serial electrocardiograms showed no significant change. Serial chest x-ray films showed progressive decrease in heart size, and cardiac fluoroscopy revealed regression to more normal contour and improved muscular excursions (Figures 8 and 9). He was discharged on March 25, 1952 with no supportive medication.

E. Chronic (Persistent) Myocarditis

There were nine cases in this group. The initial episode resembled the clinical pattern described in the benign symptomatic group, but differed in the subsequent clinical course. Irreversibility of electrocardiographic and x-ray findings was the rule. There was no complete recovery in this group. Some of the patients exhibited the chronic persistent phase as a single continuous illness. Others manifested periods of complete clinical remission requiring no medicinal support with the final recurrence being the chronic persistent episode. All of the cases presented findings of congestive heart failure. In five the condition progressed to intractable failure and they died; the remainder was symptomatically controlled on maintenance cardiac medication.

In this group two cases are presented. In one instance the chronic

FIGURE 8

FIGURE 9

Figure 8 (CASE 3) H. S.: Recurrence of cardiac enlargement of globose configuration and pulmonary congestion on re-admission.—*Figure 9* (CASE 3) H. S.: Reversal of cardiac and pulmonary changes.

persistent state was arrived at after a recurrent phase of the disease. In the other, the initial onslaught progressed to chronicity without remission.

Case 4. J. K. a 27 year old white male was admitted to the Veterans Administration Hospital, Wood, Wisconsin on December 8, 1948, with the complaints of cough, blood streaked sputum, substernal pain and hoarseness of six days' duration. Moderate fever was present. The past medical history was negative except for chronic excessive use of alcohol.

He was acutely ill. Pharyngo-tonsillitis was present. The heart was not enlarged. A gallop rhythm and apical systolic murmur were heard. Blood pressure was 120/80 mm. Hg. The pulse rate was 120 and regular. The lungs were clear. The rest of the examination was negative.

Routine laboratory studies, including sedmientation rate, were normal. Throat smears were negative for diphtheria.

The initial electrocardiogram revealed marked inversion of the T-waves in standard lead I and the left precordial leads. Admission chest x-ray film pneumonic infiltration in both mid-lung fields, with slight blunting of the left costophrenic angle. The heart was of normal size and contour.

Within a two-day period, he became afebrile and asymptomatic on supportive medication. Serial chest x-ray films showed clearing of the parenchymal lesions one week after admission, but the electrocardiographic changes persisted. Because of persistance of these changes, continued hospitalization was advised, but he felt so well that he left on December 27, 1948, against medical advice.

He returned to work, but about February 1, 1949, swelling of the ankles was evident. He was re-admitted to the hospital on February 21, 1949, in total heart failure, and anasarca was present. A gallop rhythm and systolic murmur were again noted at the apex. Routine laboratory studies were negative. The electrocardiographic pattern remained unchanged, but the chest x-ray film now revealed generalized globose cardiac enlargement with minimal pulmonary congestive changes.

The hospital course was afebrile. On a regime of bed rest, digoxin, salt restriction and mercurial diuretics a 35 pound weight loss occurred. Electrocardiographic patterns and cardiac size and contour showed gradual retrogressive changes. The clinical course was favorable, and he was permitted ambulation. He improved sufficiently by October 22, 1949 to be allowed therapeutic leave from which he failed to return.

He discontinued all medication and returned to his usual mode of living. He stated he was in good health for approximately one year until about mid-November, 1950, when he developed an upper respiratory infection with hoarseness and sore throat. Three weeks later, he again noted shortness of breath and ankle edema. When this progressed to orthopnea, he reported to Milwaukee County Dispensary on January 16, 1951, where, after failure of out-patient management, he was admitted to the Milwaukee County General Hospital on January 24, 1951.

The physical findings were essentially those of the previous admission. Congestive heart failure was present. The electrocardiogram showed progressive changes, and the heart again showed marked generalized globose enlargement. Routine laboratory studies were negative.

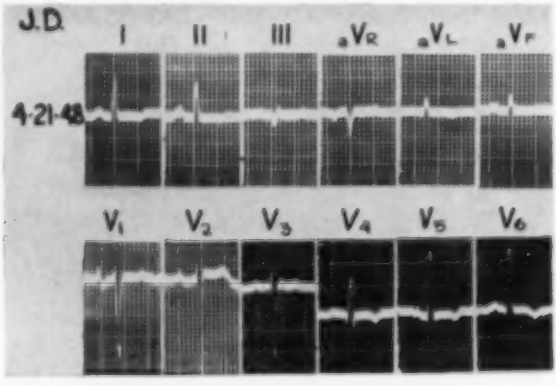

FIGURE 10 (CASE 5) J. R.: Chronic (persistent) myocarditis. Changes indicative of left ventricular strain.

The hospital course was afebrile, but progressively unfavorable. The congestive heart failure did not respond to customary management. An intensive course of penicillin was given empirically without altering the unfavorable course. Pulmonary infarction complicated the heart failure, and anti-coagulant therapy was instituted. Because of the unfavorable clinical trend, ACTH was given for 10 days. He became worse, and the drug was discontinued. He died in uncontrolled congestive heart failure one month later, on March 15, 1951.

An autopsy was performed (*AC-122-51*). On external examination, there was edema of the wrists and legs. The abdominal cavity contained 500 ccs. and each pleural cavity 200 ccs. of fluid. The heart weighed 590 grams and was rounded and flabby. Within the right auricular appendage, there was an antemortem clot. The coronary vessels were patent and elastic. Both ventricles were dilated. The liver and spleen were congested. The lungs showed multiple pulmonary infarctions.

Microscopically, the heart contained small focal scars. These areas were edematous with loose interstitial tissue. The myocardial fibers in many portions of the heart were uneven in size and had irregular nuclei.

Case 5. J. D. a 40 year old white male was admitted to the Veterans Administration Hospital, Wood, Wisconsin on March 13, 1948, with the complaints of shortness of breath and swelling of the legs of two and one half months duration. Early in December, 1947, he developed a severe respiratory infection associated with fever and cough. He improved under symptomatic treatment by his private physician, but some cough and effort breathlessness persisted. Early in January, 1948, he noticed ankle edema. Symptoms became progressively worse, and he was hospitalized. Past medical history was negative except for chronic excessive use of alcohol.

He was dyspneic and orthopneic. No fever was present. The heart border was obscured by left hydrothorax. The heart tones were distant, but not remarkable. No heart murmur was present. The rate was 122 per minute, regular rhythm, with the blood pressure of 118/84 mm. of Hg. Dullness and absent breath sounds were noted over the left lower chest. Moist rales were heard over the left upper chest and the right base posteriorly. The liver was enlarged four fingerbreadths below the right costal margin and not tender. Severe dependent edema was present up to and including the sacral area. The remainder of the examination was negative. Routine laboratory studies were normal. Sedimentation rate was normal.

The initial electrocardiogram showed a left heart strain pattern (Figure 10). The admission chest x-ray film revealed marked globose cardiac enlargement, with an extensive left pleural effusion, and pulmonary congestion (Figure 11).

On a regime of bed rest, digitalization, salt restriction and mercurial diuresis, he lost 36 pounds in seven days and 60 pounds in several weeks. Four thoracenteses were required during this period. About 2,000 cc. of fluid was removed from the left hemithorax during each procedure. There was never complete regression of electrocardiographic and x-ray film findings. He reached a clinical plateau, and while not completely free of symptoms, was discharged on August 27, 1948 with maintenance medication and markedly reduced physical regime.

FIGURE 11

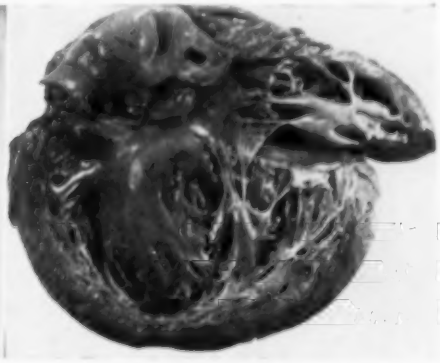

FIGURE 12

Figure 11 (CASE 5) J. D.: Marked globose cardiac enlargement with pulmonary congestion and left pleural effusion.—*Figure 12* (CASE 5) J. D.: Gross heart specimen Globose cardiac enlargement with hypertrophy and dilatation.

He was adequately controlled on maintenance therapy until shortly before re-admission when he discontinued medication of his own accord. He was re-admitted on March 8, 1949 with similar complaints and physical findings except that a systolic apical murmur was noted for the first time. Heart failure was again present, and again controlled as before. Electrocardiographic and x-ray film findings were essentially unchanged. He was discharged on July 29, 1949 on maintenance medication.

Adequate cardiovascular balance was maintained until February 15, 1950, when symptoms and signs of congestive heart failure recurred in spite of medicinal support. He was re-admitted on February 25, 1950, in uncontrolled heart failure. The findings were essentially the same as noted on previous admission, except for low grade fever. The course was progressively worsened. He died on the fifth hospital day.

An autopsy was performed (*A-53-50*). The body showed dependent edema of the lower extremities. The abdomen contained 2,000 cc. of fluid, and the right pleural cavity also 2,000 ccs. of clear fluid. The left pleural space was obliterated by fibrous adhesions. Both lungs showed marked hemorrhagic edema. The heart (Figure 12), weighed 620 grams. The pericardial sac contained 300 cc. of thin, clear fluid. The myocardium was flabby. Both ventricles were hypertrophied and dilated. The right ventricle measured 6 mm., and the left 13 mms. No gross scar was noted in the myocardium, although there were subendocardial fibrous patches. Coronary vessels showed slight arteriosclerosis. The abdominal viscera were congested.

Microscopically, the heart showed edema. Blood vessels were congested. Patches of fibrous tissue replaced the interstitial tissue as well as the myocardial fibers (Figure 13). These areas showed scattered lymphocytes and rare polymorphonuclear cells and monocytes. Some of the myocardial fibers showed degenerative changes manifested by large, irregular nuclei, granular or vacuolated sarcoplasm. The liver showed severe congestive necrosis.

V. PATHOLOGY

The pathologic changes of the heart in myocarditis were both inflammatory and degenerative. Although flabbiness of the myocardium and dilatation of the heart may suggest myocarditis, it is only microscopically that the characteristic alterations are seen. These changes may be acute, subacute or chronic. In the acute stage, focal or diffuse areas of tissue damage are found. The interstices are edematous. Leukocytic infiltration of polymorphonuclear cells, lymphocytes or monocytes involves both the

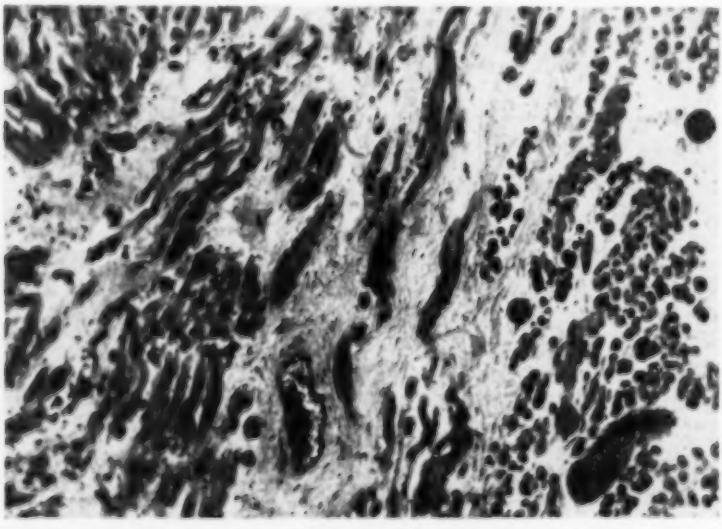

FIGURE 13 (CASE 5) J. D.: Photomicrograph (× 180). Focal fibrosis replacing interstices and myocardial fibers.

interstices and the myocardial tissue. The latter shows degenerative changes with alteration of tinctorial properties, vacuolization, granularity, loss of striations and nuclear alterations. In subacute myocarditis, lymphocytes, monocytes and fibroblasts become the inflammatory cells with areas of edema and early fibrosis. In the chronic stage, scar tissue resulting from the inflammation is indistinguishable from that produced by any other type of lesion.

VI. DISCUSSION

The wide variety of etiologic factors associated with myocarditis has been reviewed in detail by Saphir.[1] Regardless of the exciting agent, the myocardial tissue reaction is non-specific.

Diagnosis of myocarditis is based upon the recognition of myocardial involvement and the elimination of established specific etiologies for heart disease.

Certain "clinical syndromes" such as beri-beri heart disease,[15] idiopathic cardiac hypertrophy,[8, 9, 14] isolated myocarditis with myocardial fibrosis,[11, 13] heart disease of unknown etiology,[10] and cardiovascular collagenosis with parietal endocardial thrombosis,[12] have been described as distinct clinical entities. The basic pathological changes in these conditions are the same, and vary only in the relative degree of predominance of edema, cellular infiltration, necrosis, fibrosis and hypertrophy. In the present state of our knowledge, these "syndromes" should be included in the general group of myocarditis, regardless whether the cardiac manifestations are associated with an identifiable systemic disease or occur in the absence of demonstrable etiology.

The successful management of disease states which are known to cause myocarditis is the basis for effective prophylaxis. Early recognition of myocarditis and institution of appropriate supportive measures, particularly prolonged bed rest, will reduce the morbidity. When congestive heart failure is present, the usual measures for its control are indicated. Digitalis should be administered with particular caution because of frequent early manifestations of toxicity. In a limited group of cases of the recurrent or persistent type, the use of ACTH, salicylates, and antibiotics did not alter the clinical course.

SUMMARY

1. A series of 45 cases of myocarditis is presented as a clinical and pathological study.

2. A classification of myocarditis based on the clinical course, which is substantiated by pathological findings, is presented.

3. Multiplicity of etiology is discussed. In most instances, myocarditis occurs as a cardiac complication of another illness.

4. Congestive heart failure is the most common symptom complex.

5. Non-specific T-wave changes, frequently reversible, form the usual electrocardiographic findings.

6. Globose cardiac enlargement with reduced muscular excursion, also reversible in some instances, is the typical fluoroscopic cardiac contour.

7. The differential diagnosis, particularly in reference to pericarditis, rheumatic heart disease and coronary heart disease is discussed.

8. Conditions described by others as idiopathic cardiac hypertrophy, subintimal fibrosis, and nutritional heart disease may be considered to be variants of myocarditis.

9. Treatment at present consists of the management of the underlying etiological disease, bed rest, and supportive cardiac measures.

10. Clinical awareness of this entity will lead to a greater incidence of recognition and perhaps towards more effective therapeutic management.

We are indebted to Drs. Howard L. Correll and Joseph F. Kuzma for making certain cases in this series available to us for study.

RESUMEN

1. Se presenta el estudio clínico y patológico de una serie de 45 casos de miocarditis.

2. Se muestra una clasificación de las miocarditis basada en la evolucion, que está respaldada por los hallazgos patológicos.

3. Se discute la multiplicidad de la etiología. En la mayoría de los casos la miocarditis sobreviene como una complicación de otra afección.

4. El complejo sintomático más común es la insuficiencia cardiaca congestiva.

5. Hay cambios no específicos en la onda T, frecuentemente reversibles.

6. El contorno típico del corazón es el de crecimiento globuloso con expansión muscular reducida también reversible en algunos casos.

7. Se discute el diagnóstico diferencial especialmente conrelación a la pericarditis, la enfermedad cardiaca reumática y la afección coronaria.

8. Las condiciones descritas por otros como hipetrofia cardiaca idiopática, fibrosis subíntima y enfermedad cardiaca nutricia, pueden ser consideradas como variantes de la miocarditis.

9. El tratamiento actualmente consiste en el de la enfermedad causante, reposo en cama y las medidas adicionales de sostén.

10. El conocimiento de que esta entidad puede existir puede conducir a más frecuencia de su descubrimiento y probablemente a un tratamiento más efectivo.

RESUME

1. Les auteurs présentent une étude clinique et anatomo-pathologique portant sur 45 cas de myocardite.

2. Ils proposent une classification de la myocardite, basée sur l'évolution clinique et vérifiée par des constatations anatomo-pathologiques.

3. Ils discutent les diverses étiologies. Dans la plupart des cas, la myocardite survient comme complication cardiaque d'une autre affection.

4. L'insuffisance cardiaque avec stase reprèsente l'ensemble symptomatique le plus fréquent.

5. Des modifications non spécifiques de l'onde T souvent réversibles, constituent les données électrocardiographiques habituelles.

6. L'hypertrophie globuleuse du coe uravec diminution de l'expansion, également réversible dans quelques cas, est la silhouette cardiaque typiquement observée en radioscopie.

7. Les auteurs discutent le diagnostic différentiel, surtout en ce qui concerne la péricardite, le rhumatisme cardiaque et l'atteinte coronarienne.

8. Des états décrits par d'autres auteurs, comme hypertrophie idiopathique du coeur, sclérose cardiaque et affection trophique du coeur, peuvent être considérés comme des variantes de la myocardite.

9. Pour le moment, le traitement consiste dans le traitement de l'affection étiologique sous-jacente, le repos intégral au lit, et l'administration de toni-cardiaques.

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The Problem of Bacterial Resistance in Antimicrobial Therapy of Tuberculosis

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There is nothing in bacterial resistance that is not in keeping with sound biological principles. The variability of living phenomena and the ability to adapt to unfavorable and new environments is one of the most constant characteristics of life itself, and the reason for the widely dispersed living shapes and forms that inhabit this planet. Bacteria with their short life span and rapid reproduction afford one of the best opportunities for the study of genetic changes of all forms of life.

Without any pretense at a complete understanding of the mechanism of the phenomena or the laws of genetics that govern the changes, let us proceed to the problems involved concerning the resistance of Mycobacterium tuberculosis to chemical and antibiotic agents.

As new and less favorable environmental factors bear upon the bacterial cells it becomes evident that in some cells certain genes have already undergone change. These mutant cells often have the ability to survive and grow in the presence of the unfavorable influence. The rates of these changes vary according to different agents and genera of bacteria. Living bacteria seem to be constantly producing a few forms varying in one or many ways from the parent cells, and becoming susceptible to suppression or survival depending on the nature of the environmental factors.

The "resistance" of bacteria, therefore, is expressed by those altered forms that are able to survive in the presence of the antagonistic substance such as a chemical or antibiotic while the mass of the bacterial population is being destroyed. The resistant variants survive and begin to grow, producing a changed population.

These phenomena have been observed for a long time but they have been accentuated by the resistance found in various microorganisms to the sulpha drugs, penicillin, and more recently a whole category of antimicrobial substances.

The resistance of tubercle bacilli to streptomycin was observed by Youmans and Associates,[1] within a few months after streptomycin was first used, to be followed soon by many others.[2, 3] Although the antimicrobic substances were effective against the bacilli, the improvement many times came to a stop and the disease became reactivated. The resistance too frequently began within 30 days and increased to 70 per cent after four months.[4] The treatment was changed in many ways in an attempt to prevent the development of resistance with its unfavorable effects.

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Resistance to PAS was also found to develop *but* much slower and never to the same degree as to streptomycin. Carstensen[5] reported that resistance to PAS did not develop before six months. Other investigations were in general agreement.[6, 7] Resistance to isoniazid (INAH) was found to develop more quickly and more completely than to the other common drugs in use. The Medical Research Council of Great Britain[8] found that percentage resistance to INAH after one, three, and six months was 9 per cent, 64 per cent, and 97 per cent respectively.

Subsequently every other antituberculosis drug used was found to result in the development of resistance at varying rates of speed. Thus the use of viomycin, terramycin, tibione, pyrazinamide and many others have been reported to cause the emergence of bacilli of varying degrees of resistance.

The next move to counteract resistance was the use of more than one agent simultaneously. The principle underlying this procedure was that mutants resistant to two antimicrobic agents are far more rare than those resistant to only one. Instead of giving the drugs in different manners, dosages, and time intervals they were given simultaneously, with surprisingly good results. Dunner, Brown and Wallace[9] first showed the delaying action on streptomycin resistance by PAS. After 60 days only 12 per cent of the PAS and streptomycin treated cases had streptomycin resistance cultures while 50 per cent had cultures resistant to streptomycin when streptomycin was given alone. Dye[10] reported that 69 per cent of 500 cases on streptomycin alone developed resistance to streptomycin after 120 days and 53.1 per cent of 50 cases developed resistance to PAS while there was no resistance to either after 75 days of combined treatment. Many others followed with similar results. The general average of a large number of workers reveals that after four months the resistance to streptomycin was reduced from around 70 per cent to around 15 per cent and PAS from around 50 per cent to near the same low level. Sometimes the two drugs could be given for six months or a year without the development of resistance to either. Crofton[11] has shown by graphs many of these results obtained by different workers. There was a marked delay in emergence of resistance on different combinations but none seem to be as effective as the influence of PAS on streptomycin resistance.

A good illustration of the principle involved and emergence of what has been called a double mutation, has been recorded by Hobby and her associates[12] in a study of streptohydrazid, a chemical union of streptomycin and INAH. Strains resistant to both streptomycin and INAH were recovered from animals receiving streptohydrazid, as well as from animals receiving mechanical mixtures of streptomycin and INAH. The amount of streptohydrazid that is hydrolyzed in the dilutions used was, according to Pennington[13] over 98 per cent. The emergence of strains resistant to both drugs therefore, could only have been brought about by free streptomycin and free INAH. It was found that the emergence of bacilli cross-resistant to streptomycin and INAH occurs more slowly than resistance to either compound alone.

If the patient remains positive, however, the "double" mutation finally comes into play, usually before the time the bacilli have disappeared from the sputum and the patient is on the way to healing. With a "conversion" of the sputum, even if resistance develops, there is frequently such impetus given to the healing that it proceeds on toward a successful result. Within a few months after the beginning of treatment the average group of cases will reveal a conversion of 50 per cent, with the majority of the cases reaching a so-called "target-point" of healing. The remaining cases may have shown great improvement but still be positive for acid-fast bacilli. Many of these bacilli have been shown by Steenken to be avirulent[14] for guinea pigs, although D'Esopo and others[14] have found that some bacilli reported avirulent for guinea pigs still produce progressive disease in patients. There is apparently not a parallel relation betweeen the action of the bacilli on guinea pigs and on human beings.

The phenomenon of double mutation just reported seems to occur more readily when INAH is one of the two drugs in combination than with combinations of the other antituberculous agents. In fact mutation to resistance is more prone to develop toward INAH alone than to the other drugs. Middlebrook[15] states that mutation to resistance to INAH is of the order of 500 fold more than for streptomycin.

Combining INAH with streptomycin and PAS by Ferebee and Mount[16] has been reported on in the U. S. Public Health Service Study with the observation that there is a more rapid conversion of sputum by using streptomycin and INAH but the resistance in the remaining positive cases is about twice what it is when streptomycin and PAS are used together. Étienne Bernard[17] recommends that all three drugs be given together. Sweany, Perez, and Dietrich[18] compared all combinations of treatment—PAS and INAH, streptomycin and INAH and streptomycin, PAS, and INAH, but reported that there was little to choose between the three regimens so far as x-ray and clinical changes were concerned. The conclusion was that the question of giving one regimen or the other ultimately should be in favor of the one that delayed the emergence of resistance the longest. There was another important aspect and that is that it is well to hold in reserve one potent drug in case resistance develops to any or all of the drugs. Up to this moment there has been no proof that three drugs delay resistance development longer than two. The end result of administering three or more drugs requires, therefore, more work, with no better clinical result. Besides there is no hope of further treatment when resistance develops to all drugs.

In order to test the various possibilities we have been setting aside a series of far advanced cases that we felt would remain positive for a year or more and tested the development of resistance of the bacilli to the various drugs used singly and in combination. There was the advantage in this work of dealing with strains as they are encountered in practice and not on stock cultures.

In a rather large group of selected cases we were surprised that so few of the far advanced cases remained positive long enough to establish curves

of resistance. In fact, so few were left in the streptomycin and INAH series that the effects could not well be charted. Ferebee and Mount[16] had the same difficulty with a large series on these two drugs but arrived at the conclusion mentioned above, viz: that INAH with streptomycin produced more negative sputums but resistance in surviving strains was about twice as great as with streptomycin and PAS.

Of 11 cases that we were able to follow, where streptomycin, PAS, and INAH were used, there was a conversion of 81.8 per cent within 17 weeks. Of seven on PAS and INAH 71.4 per cent of conversions were found in the same period of time.

In Chart I there is a graph showing the percentages of positive cultures in 11 cases on PAS, streptomycin, and INAH, and seven cases on PAS and INAH after 4, 8, 12, 16, and 17 weeks, respectively. None of them had any previous treatment.

The remaining positive culture cases are shown in Charts II, III, IV, and V. These cases did not lend themselves to joint analysis but rather to individual reporting.

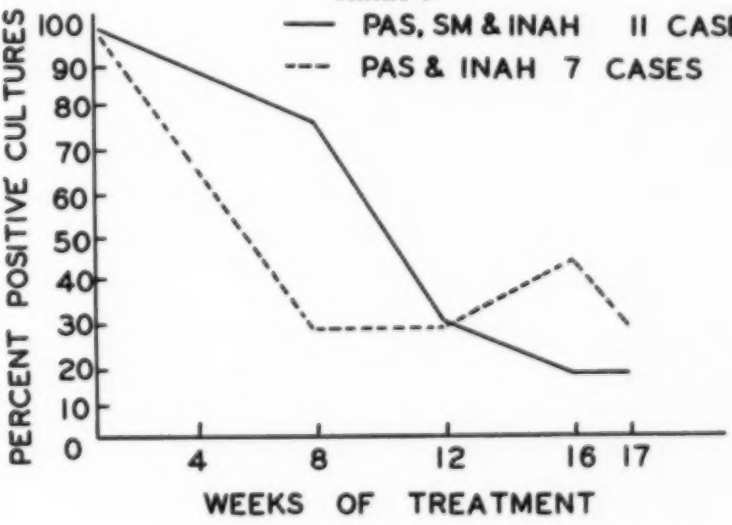
Case 1. In Chart II where all three drugs were used and numerous bacilli were present there was a development of full resistance to 5 mcgm. INAH in 12 weeks, to 10 mcgm. streptomycin in 16 weeks and to a mixture of streptomycin, 20 mcgms., and INAH, 5 mcgms., within 24 weeks. This experiment was considered reliable because all but one test was a direct test for resistance. The bacilli remained sensitive to 10 mcgms. PAS until death—45 weeks after the beginning of the experiment but all drugs were discontinued after 36 weeks. Chart II.

In *Case 2* (W. F.) full INAH resistance developed after 18 weeks when the patient left A.M.A. Sensitivity remained for streptomycin and PAS. Chart III.

Case 3 (W. H.) In the two cases remaining on a PAS and INAH regimen, one (W. H.) was partially resistant to INAH after eight weeks and remained unchanged until 20 weeks, the end of the experiment. The resistance to PAS was partly developed in nine weeks and complete in 20 weeks. Chart IV.

There was apparently no advantage obtained so far as PAS resistance was concerned but INAH resistance never fully developed during the 20 weeks of treatment.

CHART I



Case 4 (J. S.). The next case, J. S., on PAS and INAH developed full resistance to INAH after 17 weeks (or earlier, as the cultures were negative up to that time) but remained sensitive to PAS up to 32 weeks, the end of the experiment.

The findings in the four cases were not indicative of any substantial advantage

CHART II

WEEKS OF THERAPY PAS, SM & INAH	CONC SMEAR	SENSITIVITY TESTS MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
4	NUM	S	S	S	S	D
12	NUM	S	S	R	S	D
16	NUM	S	R	R	S	D
20	NUM	S	R	R	PR	D
24	NUM	S	R	R	R	I I+
28	NUM	S	R	R	R	D
36	NUM	S	R	R	R	D
DRUGS DISCONTINUED AFTER 36 WKS						
1 WEEK LATER	NUM	S	R	R	R	D
8 WEEK LATER	NUM	S	R	R	R	D
PATIENT EXPIRED 4 WKS AFTER LAST TEST						

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH

CHART III

WEEKS OF THERAPY PAS, SM & INAH	CONC SMEAR	SENSITIVITY TEST MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
2	NUM	S	S	S	S	D
6	FEW	S	S	S	S	I I+
10	NEG	CULTURE NEGATIVE				
14	FEW	S	S	PR	S	I IC
18	FEW	S	S	R	S	I 8C

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONIES

by either the three drugs together, or by PAS and INAH. Neither combination gave any better, if as good, a result as streptomycin and PAS or streptomycin and INAH.

In order to support the findings, studies were made on a group of old cases where many combinations of drugs had been given for one or more years. Sensitivities were determined and different new combinations were then given until complete resistance had developed.

Case 5 (C. G.). This case had received PAS and streptomycin for eight weeks and PAS, streptomycin and INAH for eight weeks. There was a three weeks break in treatment then treatment was resumed for 26 weeks. This made a total of 34 weeks for INAH, 42 weeks for streptomycin and PAS; there was no resistance to any of the three drugs. After 27 more weeks (61 weeks for INAH and 69 weeks for streptomycin and PAS) full resistance had developed to streptomycin and INAH but sensitivity to PAS remained for the full 69 weeks, after which cultures turned permanently negative. Chart VI. The first two courses of drugs are not shown.

This result was about the best that could be expected of any combination, but it must be emphasized that individual variation of bacillary strains may play an im-

CHART IV

WEEKS OF THERAPY PAS & INAH	CONC	SENSITIVITY TEST MCGM/ML				TEST METHOD
		PAS 10	SM 10	INAH 5	SM 20 INAH 5	
8	NUM	S	S	PR	S	D
9	NUM	PR	S	R	S	I 3+
13	NUM	PR	S	PR	S	D
16	NUM	PR	S	PR	S	D
20	NUM	R	S	PR	S	D

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH

CHART V

WEEKS OF THERAPY PAS & INAH	CONC. SMEAR	SENSITIVITY TEST MCGM/ML				TEST METHOD
		PAS 10	SM 10	INAH 5	SM 20 INAH 5	
1	NUM	S	S	S	S	D
8	NEG	CULTURE NEGATIVE				
13	NEG	CULTURE NEGATIVE				
17	FEW	S	S	R	S	I 20C
25	NUM	S	S	R	S	I 10C
32	FEW	S	S	R	S	D

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONIES

portant role. If this result was constant it would point to a tremendous advantage in giving all three drugs simultaneously.

Case 6. W. P. had received streptomycin and INAH for 12 weeks, then a break of two weeks after which PAS was added. After 45 weeks for streptomycin and INAH and 33 weeks for PAS the bacilli were sensitive on direct testing to all three drugs. After 68 weeks of streptomycin and INAH and 56 weeks of PAS partial resistance developed to SM and PAS. There is a partial resistance at present to all three drugs and the treatment is being continued. Chart VII.

Case 7. B. Mc. received 10 weeks treatment of streptomycin alone; then did not receive any more streptomycin until 17 months later, but after a lapse of one year PAS alone was given for 10 weeks. There was then five weeks of INAH and PAS. After this the patient finally was put on all three drugs. After a total of 32 weeks (much of it interrupted treatment) there was partial resistance to PAS. Full resistance to PAS was shown after 67 weeks, but may have appeared earlier as there was no test in between. After 27 weeks (of interrupted treatment) there was still sensitivity to streptomycin but partial resistance developed by 61 weeks and full re-

CHART VI

WEEKS OF THERAPY PAS, SM & INAH	CONC SMEAR	SENSITIVITY TEST MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
26	NUM	S	S	S	S	I 8C
34	NUM	S	S	S	S	I 12C
42	MOD	CULTURE NEGATIVE				
53	NUM	S	R	R	R	D
ALL CULTURES NEGATIVE AFTER 54 WKS						

D DIRECT TEST C COLONIES
I INDIRECT TEST & AVAILABLE GROWTH

CHART VII

PRIOR THERAPY — SM & INAH 12 WKS

WEEKS OF THERAPY PAS, SM & INAH	CONC. SMEAR	SENSITIVITY TESTS MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
33	NUM	S	S	S	S	D
54	MOD	CULTURE NEGATIVE				
56	NUM	PR	PR	S	S	D
61	NUM	PR	PR	S	S	D
65	NUM	PR	PR	PR	S	D

D DIRECT TEST

sistance by 70 weeks. After 22 weeks (the first test made) full resistance had developed to INAH.

It is important to note that full resistance to 5 mcgms. INAH was found after 22 weeks, and only partial resistance to 10 mcgms. streptomycin after 61 weeks, but resistance to the mixture of 20 mcgms. streptomycin and 5 mcgms. INAH did not appear until 22 weeks later, during which time the patient had received 13 more weeks of a combination of streptomycin and INAH in the form of streptohydrazid. Chart VIII.

Case 8. S. H. had an irregular and interrupted course of treatment of streptomycin and PAS for 17 weeks; PAS was then given alone for 35 weeks more because of a streptomycin reaction. There was a total of 52 weeks of PAS and then eight more weeks of streptomycin (total of 25 weeks) and 16 more weeks of PAS (total 68 weeks), and 17 weeks of INAH with full sensitivity to all drugs at the time of permanent conversion of sputum. Streptomycin was given for 25 weeks, PAS for 69 weeks and INAH for 17 weeks. This case represents an ideal plan of giving the

CHART VIII

PRIOR THERAPY — SM 10 WKS. PAS 10 WKS
PAS & INAH 5 WKS

WEEKS OF THERAPY				CONC	SENSITIVITY TEST MCGM/ML				TEST
PAS	SM	INAH	SINH	SMEAR	PAS 10	SM 10	INAH 5	SM 20 INAH 5	METHOD
17	17	17		NUM	PR	S	R	——	D
52	51	52		NUM	R	PR	R	S	D
	60		5	NUM	R	R	R	S	D
			9	NUM	R	R	PR	S	D
			13	NUM	R	R	R	R	D
			18	NUM	R	PR	R	PR	D

D DIRECT TEST

CHART IX

PRIOR THERAPY — PAS & SM 17 WKS.
PAS 35 WKS.

WEEKS OF THERAPY			CONC	SENSITIVITY TESTS MCGM/ML				TEST
PAS	SM	INAH	SMEAR	PAS 10	SM 10	INAH 5	SM 20 INAH 5	METHOD
	1	1	NUM	S	S	S	S	D
16	8	17	FEW	S	S	S	S	I IC
17	9	18	FEW	CULTURE NEGATIVE				
26	18	27	NEG	CULTURE NEGATIVE				

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONY

standard combination of streptomycin and PAS and finishing off by adding INAH. The INAH may be thrown in at the beginning in panic cases or reserved for a knock out of the more chronic types at the end. Chart IX.

Case 9. C. B. received INAH eight weeks, PAS and streptomycin five weeks and PAS and INAH until the 56th week, at which time the sputum turned positive for the first time since near the beginning of treatment. At this final test before essential conversion of sputum there was complete resistance by indirect test to streptomycin and INAH and partial resistance to PAS. The culture was still sensitive to 20 mcgms. streptomycin and 5 mcgms. INAH combined. It shows that the problem of resistance depends on the amount of drug tested against. There was apparent complete resistance to streptomycin and INAH when tested separately but sensitive to the mixture of 20 mcgms. streptomycin plus 5 mcgms. INAH. (no chart shown)

Case 10. E. B. had a record of over two years of therapy. First 32 weeks with streptomycin and PAS and then the patient was put on PAS and INAH. After 22 weeks the culture was sensitive to INAH partly resistant to PAS (54 weeks in all) and fully resistant to streptomycin (32 weeks in all). The cultures largely on indirect testing remained fully resistant to streptomycin throughout, although no more of the drug was given except for six weeks as streptohydrazid. Full resistance did not develop to PAS until 119 weeks, with 113 weeks of treatment. Full resistance to INAH did not develop until 75 weeks. It was unusual that the sensitivity to INAH remained so long. Chart X.

Case 11. C. M. received streptomycin and INAH for 38 weeks and the culture was still sensitive to all drugs. Chart XI.

CHART X

PRIOR THERAPY — PAS & SM 32 WKS.

WEEKS OF THERAPY				CONC.	SENSITIVITY TEST MCGM/ML				TEST
PAS	SINH	INAH	VIO	SMEAR	PAS 10	SM 10	INAH 5	SM 20 INAH 5	METHOD
22		22		NUM	PR	R	S	—	I 14C
56	2	56		NUM	PR	R	PR	S	I 5C
58	4	58		NUM	PR	R	PR	S	I 7C
62	6	62		NUM	PR	R	S	S	I 7C
66		66		NUM	PR	R	PR	PR	I 8C
72		72		NUM	CULTURE NEGATIVE				
75		75		NUM	PR	R	R	PR	D
79		79		NUM	PR	R	R	R	I 10C
81		81	3	NUM	CULTURE NEGATIVE				
		86	7	NUM	PR	PR	R	PR	I 3C
		87		NUM	R	R	R	R	I 45C
		90		NUM	R	R	R	PR	I 12C

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONIES

Case 12. F. S. received 5 "shots" of streptomycin before admission then was treated for 22 weeks with streptomycin and INAH at which time cultures were sensitive to all drugs. After 24 weeks the culture turned negative. Chart XII.

Case 13: C. C. received PAS and streptomycin for 24 weeks, at the end of which time the cultures were sensitive to streptomycin and partly resistant to PAS. In the

CHART XI

WEEKS OF THERAPY SM & INAH	CONC SMEAR	SENSITIVITY TEST MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
3	NUM	S	S	S	S	D
8	FEW	S	S	S	S	I 30 C
12	NEG	S	S	PR	S	I 3 C
16	NEG	CULTURE NEGATIVE				
25	NEG	S	PR	S	S	I 35 C
30	NEG	CULTURE NEGATIVE				
38	NEG	S	S	S	S	D

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONIES

CHART XII

PRIOR THERAPY – 5 INJECTIONS OF SM BEFORE ADMISSION

WEEKS OF THERAPY SM & INAH	CONC SMEAR	SENSITIVITY TEST MCGM/ML PAS 10	SM 10	INAH 5	SM 20 INAH 5	TEST METHOD
3	MOD	S	S	S	S	D
8	MOD	S	S	S	S	I 20 C
12	FEW	S	PR	S	S	I 2 C
16	MOD	CULTURE NEGATIVE				
22	NUM	S	S	S	S	I 2 C
24	FEW	CULTURE NEGATIVE				

D DIRECT TEST
I INDIRECT TEST & AVAILABLE GROWTH
C COLONIES

final test after 28 weeks the last positive culture was obtained. The bacilli were fully resistant to streptomycin after 28 weeks and still partly resistant to PAS after 24 weeks. After four weeks of INAH the bacilli were still sensitive to it and there was sensitivity to the combination of streptomycin 20 mcgms. and INAH 5 mcgms., as would be expected.

Discussion

A study was made to determine the time of emergence of resistance in a series of far advanced cases which it was thought would remain positive for at least a year and in which resistance could be studied with various drug combinations, especially streptomycin and isoniazid; para-aminosalicylic acid and isoniazid; para-aminosalicylic acid, isoniazid and streptomycin. Out of a large number of cases only 13 could be followed long enough to reveal any worthwhile information. In the completed report most of these 13 have been charted in detail. In the other cases the sputum turned negative before any worthwhile information could be obtained. In the study reported the object was also to find out, if possible, the combination of drugs that gives the best and most lasting therapeutic effect as well as the combination that delayed the emergence of resistance the longest. The clinical results on most of these cases have been reported already by Sweany, Perez, and Dietrich at the Pan American Congress of Tuberculosis held in Caracas in December, 1953. The resistance studies have been carried on before and since that time and are being reported as well as possible at this time.

The preliminary aims have not been completely realized but a few trends have been observed that may be of some use in the administration of future drug regimens.

Reports already made in the past indicate that resistance develops to isoniazid within one and a half to three months after the beginning of treatment. The resistance to streptomycin has been reported to develop in two to four months in about 70 per cent of the cases when used alone. Para-aminosalicylic acid resistance has been reported to develop in about 50 per cent of the cases when used alone within three to four months time.

In the study to be reported it has been observed that resistance develops to isoniazid within about four to six months when it is combined with other drugs. As will be seen it is about twice the time on the average required for resistance to develop to isoniazid when it is used alone. In one case treated with isoniazid in combination with streptomycin and then para-aminosalicylic acid, only partial resistance developed after 77 weeks. Streptomycin resistance has been delayed usually much longer than INAH resistance, sometimes for many months and up to a year or a year and a half. The emergence of resistance to para-aminosalicylic acid usually required the longest. In the small series reported there was only one exception where resistance developed to para-aminosalicylic acid before the other two. The resistance to this drug is usually partial and required more time to become complete, in 18 to 24 months. The delay is so consistent that no concern need be given to resistance to para-aminosalicylic acid for at least six or eight months especially when it is combined with one or more of the other drugs. Streptomycin and isoniazid are more prone

to develop resistant strains than para-aminosalicylic acid but both are delayed many months on the average by combining with the other drugs.

A feature that has been observed by clinicians is that a favorable result may be obtained long after resistance has been reported. While the "onward motion" of healing may proceed after full resistance it must be pointed out that the usual resistance tests may not indicate the disappearance of the last sensitive micro-organisms and until these last few are gone there still may be some favorable clinical effect. This does not take into consideration the possibility of avirulent bacilli left in some lesions. The problem presented by these bacilli is that they are avirulent for animals but sometimes still seem to be virulent for human beings.

To test for streptomycin and isoniazid resistance we have adopted a combination of 20 mcgms. of streptomycin and 5 mcgms. isoniazid in a mixture. Resistance to this combination appears much later than when the drugs are tested separately. For practical purposes full resistance to the above mixture rules out any chance for the drugs having the possibility of any favorable effect and under these conditions the bacilli may be considered fully and permanently resistant.

After surveying the possibilities of all combinations of the drugs the following recommendations may be offered:

First that the three drugs together while giving good results do not appreciably give any better results than the various combinations of two drugs with regard to both clinical improvement and the delay of resistance. Furthermore, when the three drugs are used and exhausted there is nothing left to rely on except less effective drugs.

It would seem that any ordinary case of pulmonary tuberculosis should be treated with streptomycin and para-aminosalicylic acid as has been used with such success in the past. A close second to this combination is para-aminosalicylic acid with isoniazid. In this manner one of the potent drugs (streptomycin or isoniazid) may be reserved for a later emergency should one develop.*

Of course, in all panic cases such as tuberculous pneumonia, meningitis, or in cases in which the time element is limited, the streptomycin and isoniazid combination has given the best results and seems to be the combination of choice. It seems to produce a more potent and rapid effect on the bacilli and causes a more rapid conversion of the sputum to negative.

As to the emergence of resistance there is still too much variability to set down any hard and fast rules. Tests for resistance must be run as long as bacilli are present. After all, treatment must be guided by the clinical result obtained. If there is still improvement, the treatment should be continued.

The problem of bacilli that are avirulent for animals is one that is going to require a great deal of study before it can be completely and satisfactorily evaluated.

*Since this article was written, the streptomycin and PAS combination has been adjudged to be less useful than some of the others. The exact place of each combination in the scale of effectiveness remains, at this time, undetermined.

SUMMARY

Resistance of tubercle bacilli to various unfavorable and environmental factors is one of the fundamental laws of biology. The resistance that develops varies with each factor and each strain of bacteria. So far as the common antimicrobial agents against tuberculosis are concerned resistance develops completely to isoniazid rather promptly within two to four months in the preponderant majority of strains—to streptomycin about 70-80 per cent and to para-aminosalicylic acid about 50 per cent. By combining the three drugs in different combinations emergence of resistance is delayed, due to what is thought to be a double mutation which is found to be much rarer than the mutants resistant to the drugs individually. Accordingly streptomycin and isoniazid together prolonged the emergence of resistance at least to twice the time of either of the drugs alone, sometimes much longer. Streptomycin and para-aminosalicylic acid together prolong the time of the emergence of resistance several fold. Para-aminosalicylic acid and isoniazid also prolong the development of resistance much longer than when the respective drugs are used separately, and even longer than any other combination studied. From the meager data at hand the combination of the three drugs together does not seem to offer any advantages not possessed by the various two drug combinations. Furthermore, there is the advantage of having a potent drug available if resistance should develop to any two. A plan of treatment has been suggested based on our knowledge up to this time, that would use Sm and INAH in critical or panic cases; Sm and PAS in ordinary pulmonary tuberculosis and ordinary complications; and INAH and PAS where resistance has developed for Sm.

RESUMEN

Una de las leyes fundamentales en Biología es la resistencia del bacilo de la tuberculosis a los diversos factores desfavorables y ambientales.

Hasta ahora, en lo referente a los agentes antimicrobianos comunes contra la tuberculosis la completa resistencia contra la isoniacida se desarrolla pronto, dentro de dos a cuatro meses en la mayoría preponderante de las cepas; a la estreptomicina en el 70-80 por ciento de las cepas y al ácido paraminosalicílico en el 50 por ciento. Combinando las tres drogas de modos diversos la aparición de la resistencia se retarda debido a los que se cree sea una doble mutación que se encuentra que es mucho más rara que las mutaciones resistentes a las drogas aisladamente. De acuerdo con esto, la asociación estreptomicina-isoniacida prolongó la aparación de la resistencia cuando menos por tiempo doble que cuando se usó una sola y veces más.

La asociación estrepto-PAS prolongó tiempo de la emergencia de la resistencia varias veces más. PAS-isoniacida asociadas también prolongan la aparición de resistencia mucho más que separadas y aún más que cualquiera otra combinación usada aparte. De los escasos datos obtenibles no parece haber ventaja de la asociación de las tres drogas para prolongar la aparición de resistencia. Además hay ventaja en tener una droga dis-

ponible si se presenta resistencia a las otras dos. Se ha sugerido un plan de acuerdo con lo obtenido hasta ahora que usaría SM-INAH en los casos críticos o de pánico; SM-PAS en la tuberculosis ordinaria con sus complicaciones ordinarias y PAS-INAH cuando hay resistencia a la Estreptomicina.

RESUME

La résistance du bacille tuberculeux à différents facteurs défavorables, et aux conditions du milieu est une des lois fondamentales de la biologie. La résistance qui se développe varie selon chaque facteur et chaque souche de bactéries. En ce qui concerne les agents antimicrobiens habituellment utilisés contre la tuberculose, la résistance complète à l'isoniazide se développe assez rapidement, en moins de 2 à 4 mois, dans la grande majorité des souches, la résistance à la streptomycine dans environ 70 a 80% des souches, et la résistance au P.A.S. dans environ 50% des souches.

En associant ces trois produits en différentes combinaisons, le risque de résistance est retardée. On pense que la cause en est une double mutation, qu'on voit plus rarement que la résistance à un produit isolé. En conséquence, l'association de streptomycine et l'isoniazide retarde l'apparition de la résistance d'au moins deux fois le temps qu'il faudrait pour qu'apparaisse la résistance à chaque produit séparément, et que que fois plus longtemps encore. L'association de streptomycine et de P.A.S. retarde le temps d'apparition de la résistance de plusieurs fois le temps qu'il faudrait pour qu'apparaisse la résistance à chaque produit pris isolément. L'association de P.A.S. et d'isoniazide retarde aussi le développement de la résistance bien plus longtemps que lorsque les produits sont utilisés séparément et souvent plus longtemps que pour n'importe quelle autre association.

D'après le petit nombre de données qu'ont les auteurs il ne leur semble pas que l'association des trois produits offre aucun avantage qui ne soit déjà acquis par les associations de deux produits différents. En outre, il y a un avantage à avoir un produit efficace valable au cas où une résistance se développerait à l'un des deux produits. Les auteurs proposent un programme de traitement basé sur leurs connaissances actuelles, qui admettent que la streptomycine et l'isoniazide associées ne devraient être utilisées qu'en cas de phase aiguë ou dangereuse. La streptomycine et le P.A.S. devraient être le traitement de la tuberculose pulmonaire commune, ou des Complications communes, l'isoniazide et le P.A.S. ne devraient être utilisées qu'en cas de résistance à la streptomycine.

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Congenital Pulmonary Agenesis

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In commenting upon the genesis of the lung, Gruenfeld and Gray state that "developmental anomalies of the lung is favored by the phylogenetic newness of this organ and the enormous growth it must undergo in the embryo before its functional form is achieved." These authors classify the maldevelopment of the lung as follows:

A—Deficiency in development of the lungs.
- 1—Absence of both lungs
- 2—Agenesis of one lung
- 3—Abnormalities in the branchings of the stem bronchi
- 4—Cystic disease and so-called congenital bronchiectasis.

B—Excessive formations in the development of the lungs.
- 1—Azygos lobe
- 2—Supernumerary lobes
  - a—Tracheal lobe
  - b—The so-called lower accessory lobe
  - c—Ectopic lung.

The rarity of agenesis of the lung is attested to by the infrequency with which it has been reported in the literature. As of January 1, 1954, there were less than 150 cases reported in medical journals. In a review of 100 cases (96 from the literature and four reported in this paper) there were 40 males and 38 females. In 22 the sex is not mentioned. The right lung was involved in 48 and the left in 52. The age distribution in 86, in which it was mentioned, was as follows: premature, seven; birth to one week, six; one week to one month, eight; one month to three months, three; three months to six months, nine; six months to one year, six; one year to two years, 10; two to five years, eight; five to 15 years, six; 15 to 25 years, eight; 25 to 35 years, three; 35 to 50 years, six; 50 to 65 years, four, and 65 to 72 years, two.

Symptoms in patients with congenital pulmonary agenesis are variable, from complete absence to those of marked cardiorespiratory embarrassment. When symptoms do occur, they are not necessarily due entirely to the agenesis, but may also be due to associated malformations and complications. The most frequent symptoms encountered in patients with

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clinical manifestations of pulmonary agenesis are dyspnea and tachycardia, occasionally accompanied by stridor and cyanosis. The commonest thoracic physical findings are *symmetry of the chest* and some respiratory lag of the affected side. The involved side usually is *not* smaller than the uninvolved side. Such findings in the young subject with progressive respiratory distress, should make one highly suspicious of agenesis of the lung. This is particularly true when it is accompanied by displacement of the heart, trachea, and mediastinum to the affected side and there is elevation of the diaphragm on that side. The degree of displacement of these structures varies with the degree of pulmonary agenesis. Roentgenographic studies of the thorax confirm physical findings. Absence of asymmetry of the chest and displacement of structures as mentioned in the foregoing are cardinal findings in pulmonary agenesis. Bronchoscopic and bronchographic variants are many. In general, however, they disclose rudimentary development of the bronchial tree on the affected side, and distortion and displacement of the bronchial tree on the uninvolved side.

Case 1: A five pound, eight ounce newborn female infant, delivered spontaneously at full term, began to show signs of respiratory distress soon after birth. Accessory muscles of respiration were very active. Breath sounds were harsh and accompanied by crackling rales over the right hemithorax. Heart sounds were distant and heard best in the right hemithorax. A roentgenogram of the chest revealed the heart and mediastinum in the right hemithorax and a diffuse nonaerated opacity over the greater part of the upper right lung field, Fig. 1.

Bronchoscopy revealed the trachea and both main bronchi obscured by frothy clear mucus. Except for some displacement of the left main bronchus to the right, it was otherwise not remarkable. The right main bronchus, on the other hand, appeared to be a direct downward continuation of the trachea. The orifices of the right upper and middle lobes could not be identified. The child improved after bronchoscopy, but died in respiratory distress 48 hours after birth.

At necropsy, the left lung was essentially normal, although somewhat distended. The right lung was constituted of but one lobe having a single bronchus which took the course of a normal right lower lobe bronchus, Fig. 2. The intrapulmonic subdivisions of the bronchus corresponded to that of a normal right lower lobe bronchus

FIGURE 1

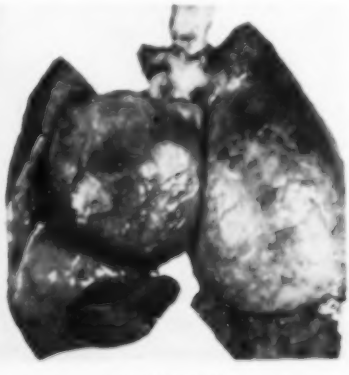

FIGURE 2

Figure 1: Opacity of the upper two-thirds of the right hemithorax with retraction of the heart and mediastinum into that area as is characteristically found in agenesis of the (right) lung. Same case as Fig. 2.—*Figure 2:* Anterior view of the intrathoracic contents as seen at necropsy in agenesis of the right lung. The heart is completely displaced to the right of the midline. The right lung is comprised of only the lower lobe. Same case as Fig. 1.

and did not present any evidence of an intrapulmonic subdivision of the right main bronchus.

The esophagus was constituted of two separate segments. The upper portion formed a continuation of the pharynx in the normal manner, but ended blindly at about 1 cm. from its origin. The lower segment originated in the region of the bifurcation of the trachea and ended by opening into the stomach below. The kidneys were fused to form a solitary horseshoe kidney.

Case 2: A seven year old child entered the hospital with a diagnosis of situs inversus. According to the mother, the heart was known to be on the right side for some time.

Examination revealed a well nourished, well developed, cooperative male child. The trachea was deviated to the right of the midline. There was dullness to percussion over the greater part of the right anterior part of the thorax. In the same area the breath sounds were distant and bronchial. The point of maximum cardiac pulsation was 5 cm. to the right of the midsternal line in the third and fourth intercostal spaces. Roentgenographic examination of the chest showed the heart retracted into the right hemithorax, the trachea deviated to the right, the left lung was emphysematous, and the right hemithorax was somewhat smaller than the left. Bronchoscopy showed nothing remarkable in the left bronchial tree. However, on the right side there was absence of the upper and middle lobe bronchi. The bronchus to the lower lobe was wider than normal, but otherwise was not remarkable.

Case 3: A 19 year old man entered the hospital for bronchoscopy because he had a 'shadow in the chest'. This condition was discovered during a routine x-ray film examination of the chest. The only significant history relative to the patient's thorax was that he would cough and had mucopurulent expectoration after exercise.

Examination revealed the following positive findings: (1) increased dullness to percussion over the right side of the chest both anteriorly and posteriorly, (2) increased tactile and vocal fremitus over the right upper half of the chest posteriorly, (3) bronchial breathing and hyper-resonance to percussion over the left side of the thorax, and (4) the point of maximum cardiac impulse was in the right anterior fourth intercostal space. The admission roentgenogram of the chest disclosed narrowing of the intercostal spaces on that side. The heart and trachea were completely within the right hemithorax.

In view of the history and x-ray findings it was thought that he had a nonopaque foreign body in the bronchus and that he should be bronchoscoped. Accordingly, this was performed but was unsuccessful because of the copious secretions in the right main bronchus which could not be removed satisfactorily by repeated aspirations via the bronchoscope. Bronchoscopy reinstituted after several days of postural drainage revealed a moderate amount of mucopurulent secretion in the left main bronchus. The subdivisions of the left bronchial tree were otherwise negative. The right main bronchus also contained a moderate amount of mucopurulent secretion. When these secretions were removed it was noted that the orifice to the lower lobe was markedly stenosed by mucosal edema. The upper and middle lobe orifices could not be visualized.

Tomography after instillation of lipiodol into the bronchial tree on the right side disclosed marked angulation of the right main bronchus posteriorly and substantiated the diagnosis of absence of the bronchi to the upper and middle lobes on the right side, Fig. 3. In view of the fact that the roentgenograms did show lung tissue in the upper part of the right hemithorax, although unaerated and possible nonfunctioning, it was deemed advisable to explore the thorax and remove the pathological tissue, if found. At the time of the operation it was noted that the right upper and middle lobes were absent and that the superior segment of the lower lobe was emphysematous, the basilar segment was indurated and contained many cystic areas. Concurrently with the absence of the upper and middle lobes the arteries and veins to those lobes were also absent.

Case 4: A 35 year old man entered the hospital in September 1952 in a moribund condition as a result of a head injury sustained in an automobile accident. He died soon after admission. Necropsy, Fig. 4, revealed absence of the right lung. At the site of the supposed origin of the right main bronchus, there was a heaping up of bronchial tissues.

CONCLUSIONS

Although pulmonary agenesis is an uncommon condition, it warrants consideration in all patients whose clinical course is not readily explainable on some other more satisfactory basis. This is particularly true in younger subjects. The frequency with which one encounters other mal-

formations in patients with pulmonary agenesis has led Ferguson and Neuhauser to explain the genesis of this condition on the basis of a defect in the germ plasm. Wexels observed that nearly 50 per cent of the patients with pulmonary agenesis have other defects. He lists these anomalies as —patent ductus arteriosus, patent foramen ovale, atresia ani, atresia of the esophagus, short bowel, atresia urogenitalis, exencephaly, horseshoe kidney, ventricular defect, hypoplasia of the face, hare lip and cleft palate, absence of the left diaphragm, absent left hand, absence of right radius, bifid uvula, spina bifida, wedge-shaped vertebrae, hemivertebra, deformed ribs, accessory thumb, closed foramen epiploica, rudimentary atlas, deformed external ear, congenital ptosis of both eyelids, small left scapula, and pulmonary veins entering the azygos vein.

Pulmonary agenesis is not incompatible with life. Twenty-three patients (27 per cent) of the present series were known to have lived to be between 15 and 72 years. In reviewing the literature regarding age and agenesis, we were impressed with the fact that those who were known to have pulmonary agenesis in early life survived it only because the associated anomalies and complications were not incapacitating. Agenesis in the patient over 15 years of age is, in all likelihood, unassociated with other malformations which are of clinical significance. On the other hand, pulmonary agenesis in early life, which is clinically manifest, is often associated with other malformations which make the condition incompatible with life.

All patients who are suspected of having pulmonary agenesis should be investigated thoroughly before being subjected to any thoracic surgical procedure. A relatively minor procedure in such a patient may terminate fatally because of the lack of appreciation of the significance of the other anomalies.

FIGURE 3

FIGURE 4

Figure 3: Roentgenogram of the chest in a patient with pulmonary agenesis of the right side.—*Figure 4:* Anterior view of the intrathoracic contents in a patient with agenesis of the right lung.

CONCLUSIONES

Aunque la agenesia pulmonar es un padecimiento poco común, amerita ser considerado en todos aquellos pacientes cuyo curso clínico no es facilmente explicable sobre otras bases más satisfactorias. Esto es particularmente cierto en los sujetos más jóvenes. La frecuencia conque uno encuentra otras malformaciones en pacientes con agenesia pulmonar, ha llevado a Ferguson y Neuhauser a explicar la génesis de este padecimiento sobre las bases de un defecto en el plasma germinal. Wexels observó que muy cerca del 50% de los pacientes con agenesia pulmonar tienen otros defectos. Cita las siguientes anormalidades: persistencia del conducto arterioso, persistencia del agujerooval, atresia anal, atresia esofágica, egenesia intestinal, atresia urogenital, anencefalia, riñón en herradura, defectos ventriculares, hipoplasia de la cara, labio leporino y paladar hendido, ausencia del diafragma izquierdo, ausencia de mano izquierda, ausencia de radio derecho, úvula bífida, espina bífida, vértebras en cuña, hemivértebras, costillas deformadas, pulgar supernumerario, ausencia de hiato de Winslow, atlas rudimentario, deformación del oído externo, ptosis palpebral congénita, escápula izquierda pequeña y venas pulmonares que desembocan a la vena acigos.

La agenesia pulmonar no es incompatible con la vida. Veintitres pacientes (27%) de las series que ahora se presentan se sabe que vivieron hasta llegar de 15 a 72 años. Revisando la literatura respecto a edad y agenesia, nos ha impresionado el hecho de que aquellos en quienes se sabía presentaban agenesia pulmonar en los primeros años de su vida, sobrevivieron a ésta sólamente porque las anomalías asociadas y complicaciones no fueron incapacitantes. La agenesia en un paciente mayor de 15 años de edad con toda posibilidad no está asociada con otras malformaciones que sean de significado clínico. Por otro lado, la agenesia pulmonar a temprana edad que es manifiesta clínicamente, está a menudo asociada con otras malformaciones que hacen el padecimiento incompatible con la vida. Todos los pacientes sospechosos de tener agenesia pulmonar deben ser investigados minuciosamente antes de ser sometidos a cualquier procedimiento quirúrgico de tórax. Un procedimiento quirúrgico relativamente pequeño en tales pacientes puede terminar fatalmente, debido a la falta de apreciación de la magnitud de las otras anomalías.

RESUME

Bien que l'agénésie pulmonaire soit un état peu habituel, elle demande à être prise en considération chez tous les malades dont les manifestations cliniques ne peuvent pratiquement pas s'expliquer par une autre cause plus satisfaisante. Ceci est spécialement vrai chez les sujets jeunes. La fréquence avec laquelle on rencontre d'autres malformations chez les malades atteints d'agénésie pulmonaire a conduit Ferguson et Neuhauser à l'expliquer par un défaut du plasma germinatif. Wexels observa que près de 50% des malades atteints d'agénésie pulmonaire présentaient d'autres malformations. Il les dénombra: persistance du canal artériel, persistance du trou de Botal, atrésie anale, atrésie oesophagienne, brièveté intestinale,

atrésie urogénitale, exencéphalie, rein en fer à cheval, atteinte ventriculaire, hypoplasie de la face, bec de lièvre et division du voile du palais, absence de diaphragme gauche, absence de main gauche, absence de radius droit, spina bifida, vertèbres cunéiformes, hémivertèbres, côtes déformées, pouce en surnombre, hiatus de Winslow comblé, atlas atrophié, oreille externe déformée, blépharoptose congénitale bilatérale, déformation scapulaire gauche, veines pulmonaires en communication avec la veine azygos.

L'agénésie pulmonaire n'est pas incompatible avec la vie. 23 malades (27%) du groupe étudié vécurent de 25 à 72 ans. En faisant la revue de la littérature en ce qui concerne l'âge et l'agénésie, les auteurs furent frappés du fait que ceux qui étaient connus comme ayant une agénésie pulmonaire depuis l'enfance, survécurent parce que les anomalies et complications associées n'entrainaient pas une impossibilité d'existence. L'agénésie chez le malade de plus de 15 ans n'est pas associée, en général, à d'autres malformations cliniquement notables. Pendant le premier âge, l'agénésie pulmonaire cliniquement évidente, est souvent associée à d'autres malformations qui rendent l'état incompatible avec la vie.

Tous les malades suspects d'être atteints d'agénésie pulmonaire devraient être examinés complètement avant que soit tentée toute intervention chirurgicale thoracique. Une opération relativement peu importante peut avoir, chez, un tel malade, une conséquence fatale, parce qu'on n'a pas apprécié la valeur des autres anomalies.

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The Diagnostic Use of Artificial Pneumoperitoneum*

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Artificial pneumoperitoneum is a procedure with which doctors are familiar, particularly in respect to its therapeutic application in pulmonary tuberculosis and chronic diffuse pulmonary emphysema. Diagnostic use of the procedure in lesions of or near the diaphragm is well known to chest physicians and surgeons, yet some general practitioners, surgeons and radiologists have remained hesitant to utilize pneumoperitoneum as a part of their diagnostic armamentarium. This is no doubt due to relative unfamiliarity with the technic of the procedure and overemphasis in the medical literature of the dangers, contraindications, and complications of induced pneumoperitoneum. As chest physicians for whom the induction of pneumoperitoneum holds little fear, we are in a position to acquaint our fellow practitioners in other specialties with the relative benignancy of the procedure as well as its wide applicability in a variety of clinical situations. It is our aim to review herein briefly some of these applications.

Jacobaeus,[1] in 1913, first suggested the use of pneumoperitoneum to provide contrast for roentgen visualization of the abdominal viscera, and Orndoff,[2] in 1919, reported his experience with this method in more than 100 cases with lesions of the upper abdominal viscera. It has been used with success in suspected subdiaphragmatic abscess. Sante,[3] four years later, reported the case of a young man with perinephric abscess complicated in the postoperative period by right pleural empyema, in whom hiccup and abdominal pain appeared. The right diaphragm was seen to be elevated on chest x-ray inspection and a strong clinical suspicion of right subdiaphragmatic abscess was entertained. Artificial pneumoperitoneum was induced, after which roentgenograms revealed a completely free space, containing air, between the liver and the right diaphragm. Thus, this procedure satisfactorily ruled out subdiaphragmatic abscess, abdominal exploration was avoided, and right thoracotomy was performed for the empyema, resulting in cure.

In this same paper, Sante advocated utilizing pneumoperitoneum in distinguishing cardiospasm from malignancy of the lower esophagus or cardiac portion of the stomach. He stated that, in cardiospasm, esophageal constriction occurs at the level of the diaphragm with a dilated sac above, and no involvement of the region between the diaphragm and cardiac orifice of the stomach, this being well seen with the aid of pneumoperitoneum. In carcinoma of the esophagus or cardiac stomach a constriction and irregularity may be seen with barium meal, but the extent of the

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lesion may not be appreciated until pneumoperitoneum is also utilized. This often demonstrates a mass in the area between the diaphragm and the cardiac stomach, serving to differentiate malignancy from a benign lesion.

Thirty years later, Meneghini and De Marchi[4] again advocated a barium meal and pneumoperitoneum combined in the study of lesions in this region. They gave pneumoperitoneum of 1000 to 1500 cc. of oxygen, and immediately had the patient ingest semi-dense barium, fluoroscopy then being performed in various positions. In their report of seven cases, the authors felt that this combination is superior to either a barium swallow

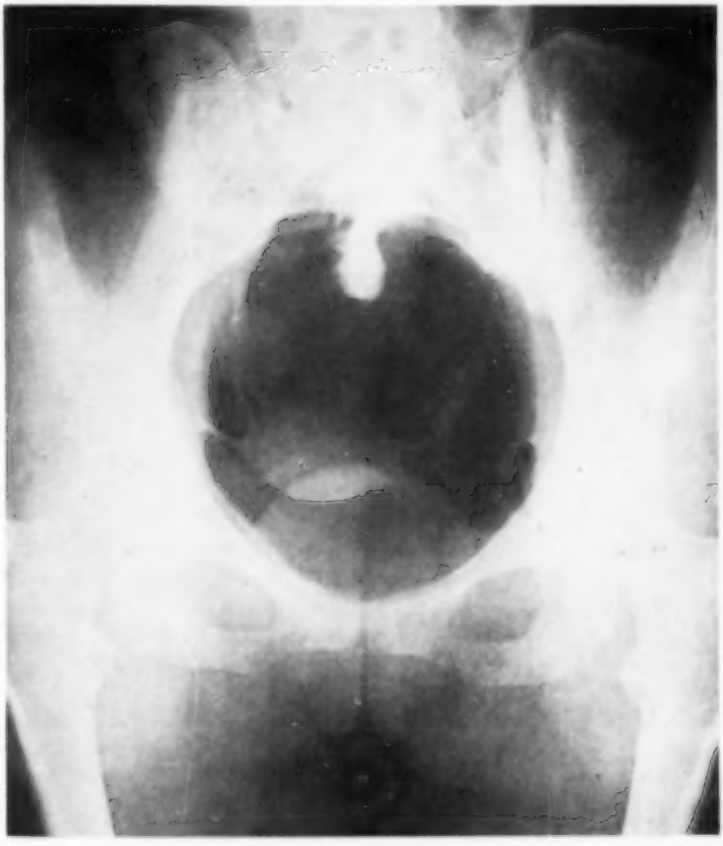

FIGURE 1: Pneumo-roentgenogram of the pelvis of a 30 year old woman who is receiving pneumoperitoneum therapy for pulmonary tuberculosis, and who has had vague right lower quadrant pain. Pelvic examination was unsatisfactory because of the presence of the pneumoperitoneum. This film shows the uterus to be normal in size and shape, and both fallopian tubes and the left ovary to be normal. The right ovary is slightly enlarged, and may represent a cystic condition. In view of the normal size of the fallopian tubes it was felt that tuberculous salpingitis was ruled out, so that pelvic surgery could be safely deferred. We feel that this diagnostic study saved the patient unnecessary laparotomy.

or pneumoperitoneum alone, especially in the study of malignant tumors of the cardia. They state it permits evaluation of the presence and degree of extension of the lesion into surrounding structures, as well as the existence of adhesions between the stomach and diaphragm. This information aids in assessing operability and deciding upon operative approach.

Pneumoperitoneum has been recommended as an auxiliary method in the diagnosis of early exudative tuberculous peritonitis by Deloff.[5] He points out that quantities of peritoneal fluid of less than 1000 cc. cannot be definitetly detected by ordinary clinical and radiographic means, but that, after pneumoperitoneum of 500 to 600 cc. of air, as little as 300 cc. of fluid can be detected by gurgling during insufflation of gas, succussion splash, and x-ray inspection showing a fluid level. We have not used pneumoperitoneum in this way, however, since it seems that paracentesis abdominis will usually provide an answer.

Visualization of the pelvic viscera, using carbon dioxide as the contrast medium, was first described by Alvarez[6] in 1921, and several papers have since appeared on this subject. The procedure was utilized by Stein[7] in the demonstration of tubal pregnancy, and its value has again been stressed by Gershon-Cohen and Hermel[8, 9] as an aid in the diagnosis of subserosal uterine tumors, bicornate or double uterus, and in the visualization of ovarian or tubal masses which may be too small to be disclosed by bimanual pelvic examination. They performed pelvic x-ray examination upon 30 female tuberculosis patients receiving pneumoperitoneum therapy, and studied the pelvic organs thus visualized, publishing their findings in 1952 and 1953 with many beautifully clear reproductions of these roentgenograms. They found normal pelvic organs on such films to have the following dimensions: fallopian tubes—3 to 6 mm. thick; uterus —5 to 7 cm. wide and 3 to 5 cm. thick; and ovaries—2 to 4 cm. long and 1.5 to 3 cm. thick.

With the bladder and rectum empty, pneumoperitoneum of 500 to 1000 cc. is instituted by the transabdominal or transvaginal route, as for the Rubin test of tubal patency. The patient is placed prone on the x-ray table with two pillows beneath the thighs, and an air pillow beneath the epigastrium, so the pelvis is elevated with the patient in a modified knee-chest position. The x-ray beam is angled through the pelvic canal axially, and three films taken directed at 10, 20, and 35 degrees cephalad. The Potter-Bucky diaphragm is used, preferably with a 16:1 grid ratio. Average roentgenographic factors are: 80 KV, 300 MAS, 40 inch target-film distance, and par speed intensifying screens. They feel the procedure is contraindicated in ruptured tubal pregnancy, and do not use the transuterine route during pregnancy, vaginal bleeding, acute cervicitis, or pelvic inflammatory disease.

Kunstadter and his associates,[10] in 1953, reported the application of pelvic pneumoperitoneum in the diagnosis of sex-endocrine disturbances. They studied 17 patients, whose ages varied from 11 weeks to 23 years, by means of pelvic x-ray inspection after the introduction of 500 cc. of carbon dioxide transabdominally. Among this group were seven cases of

ovarian agenesis, one of hypopituitarism, two of pituitary hypo-ovarianism, one of cystic ovary, two of constitutional sexual precocity, and four of pseudohermaphroditism. One of the latter was an 11 week old infant, in whom the procedure was performed without untoward effect, and clearly demonstrated female pelvic organs. The authors suggest that pelvic pneumoperitoneum may aid in diagnosis when clinical and laboratory study is inconclusive and early diagnosis is important to plan future management, thus avoiding laparotomy.

Carman and Fineman,[11] in 1924, reported the use of pneumoperitoneum as an aid in the diagnosis of diaphragmatic hernia. Bockus,[12] in his textbook on gastro-enterology, does not mention pneumoperitoneum as an auxiliary diagnostic method in his extensive discussion of diaphragmatic hernia. Eventration of the diaphragm, hiatus (esophageal) hernia, and large (non-hiatus) hernia can usually be diagnosed satisfactorily by the usual chest x-ray film, barium meal, barium enema, and characteristic history, with no need for pneumoperitoneum.

More recently, however, Stewart[13] described three patients with parasternal omental hernia, emphasizing the use of pneumoperitoneum as an accessory diagnostic aid. These hernias present themselves roentgenographically as a density in either cardiophrenic angle on the chest film,

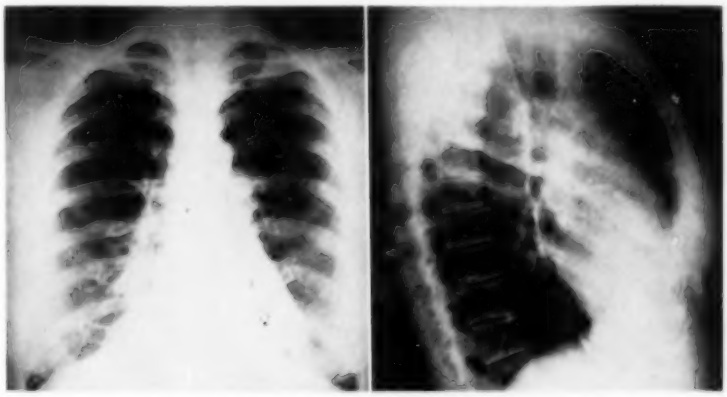

FIGURE 2A FIGURE 2B

Figure 2A: From a postero-anterior chest x-ray film of a 45 year old woman with chronic cough of five years duration, the film showing a homogeneous density at the right cardiophrenic angle.—*Figure 2B:* Right lateral view of same patient showing that the density is anteriorly overlying the heart shadow, in the region of the right middle lobe.—*Figure 2C:* Right bronchogram seen on lateral view in same patient after instillation of lipiodol, demonstrating bronchiectasis and atelectasis of the right middle lobe.—*Figure 2D:* Postero-anterior chest x-ray film of same patient after pneumoperitoneum had been established. This shows that air has entered the area of the cardiophrenic angle density, demonstrating a fairly large hernia of the foramen of Morgagni. —*Figure 2E:* Right lateral view of this patient with pneumoperitoneum present, showing the air-filled hernia sac lying anteriorly. Exploratory thoracotomy on the right was then performed, an atelectatic right middle lobe was removed which was found to contain extensive bronchiectasis, and the diaphragmatic hernia of the space of Morgagni was repaired.

FIGURE 2E

FIGURE 2D

FIGURE 2C

and must be differentiated from benign or malignant neoplasms (mediastinal or pulmonary), aberrant thyroid, and embolic, inflammatory, or atelectatic lung lesions. In one patient, pneumoperitoneum resulted in the appearance of air in the hernial sac on x-ray film. He suggests that pneumoperitoneum will have its greatest usefulness in cases in which barium enema studies fail to demonstrate cephalad and anterior displacement of the transverse colon.

Rowles and Crenshaw,[14] in 1953, described nine thoroughly studied patients with diaphragmatic herniation through the space of Morgagni, six of whom were successfully repaired at thoracotomy. In one of them, upper gastro-intestinal x-ray films, barium enema, and x-ray film of the chest with pneumothorax and pneumoperitoneum were all negative. However, in two, in whom operation was not done, pneumoperitoneum demonstrated clearly the presence of air in the hernial sac, providing reassurance that the lesion was of benign nature.

As a rule, the diagnosis of tumor of the diaphragm can be strongly suspected from the appearance of the chest x-ray film, and the chest surgeon is led to promptly explore the chest surgically. Occasionally the picture may be suggestive of diaphragmatic hernia or elevation of the diaphragm from an intra-abdominal disorder. Induction of pneumoperitoneum will tend to rule out these latter conditions, and may outline quite clearly the size and density of the lesion and its intimate connection with the diaphragm, making preoperative diagnosis more definite.

FIGURE 3A FIGURE 3B

Figure 3A: From a postero-anterior chest x-ray film of a 35 year old woman in whom a survey film revealed a rounded density in the left diaphragm. She had no symptoms relating to the chest or the gastro-intestinal system.—*Figure 3B:* Left lateral view taken at the same time, showing the density to be lobulated and situated anteriorly. Fluoroscopy of this patient after pneumoperitoneum revealed the density to appear solid and containing no air (no film available). Barium meal was normal. Left thoracotomy was done and a large, multiloculated, fluid filled cyst was found to be attached to the left diaphragm. This was removed, and she made an uneventful recovery.

SUMMARY

1. Artificial pneumoperitoneum may be applied as a diagnostic aid in a variety of clinical situations, as in:

a) Suspected subdiaphragmatic abscess.
b) Lesions of the cardiac portion of the stomach, when the pneumoperitoneum is combined with a barium meal.
c) The detection of ascites, when the amount of fluid is small.
d) The study of pelvic organs of adult females.
e) The study of sex-endocrine disorders.
f) The study of patients whose chest x-ray films show densities lying in the lower thorax in contiguity to the diaphragm.

2. As chest physicians, we are familiar with the technic of artificial pneumoperitoneum and thus may be of aid to our fellow practitioners in other specialties in encouraging the use of this helpful procedure.

RESUMEN

1. El neumoperitoneo artificial puede usarse como recurso diagnóstico en una serie de situaciones clínicas tales como:

a) Sospecha de absceso subfrénico,
b) Lesiones de la porción cardial del estómago cuando el neumoperitoneo es combinado con una comida de bario.
c) El descubrimiento de ascitis cuando la cantidad de líquido es pequeña.
d) El estudio de los órganos pélvicos en las mujeres adultas.
e) El estudio de los trastornos sexuales endócrinos.
f) El estudio de los enfermos cuyas radiografías muestran opacidades en el tórax cerca del diafragma.

2. Como especialistas del tórax, estamos familiarizados con la técnica del neumoperitoneo artificial y así podemos ayudar a nuestros colegas, médicos de otras especialidades para alentar el uso de este procedimiento útil.

RESUME

1. Le pneumopéritoine artificiel peut être utilisé dans plusieurs cas cliniques dans un but diagnostique; il en est ainsi:

a) lorsqu'on suspecte un abcès sous-diaphragmatique;
b) pour des lésions gastriques localisées au cardia; il y a lieu alors de combiner le pneumopéritoine avec le repas baryté;
c) pour la découverte d'ascite, lorsque la quantité de liquide est faible;
d) pour l'étude des organes pelviens chez les femmes adultes;
e) pour l'étude des troubles des glandes endocrines génitales;
f) pour l'étude des malades chez lesquels les radiographies montrent des ombres de la partie inférieure du thorax, qui semblent contiguës du diaphragme.

2. Les auteurs font remarquer que les médecins spécialisés en affections thoraciques qui sont par conséquent familiarisés avec la technique du pneumopéritoine artificiel, peuvent aider leurs collègues des autres spécialités en les engageant à utiliser ce précieux procédé.

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Combined Therapy in Pulmonary Tuberculosis

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Introduction

There has been considerable discussion concerning the most advantageous method of using isoniazids, which are now accepted by almost the entire world as a useful drug in the treatment of pulmonary tuberculosis. In 1952, when Robitzek, Selikoff and Ornstein[1] first reported their experience in humans with pulmonary tuberculosis, they had used isoniazids in cases where streptomycin had previously failed. In fact, those used were not simple cases, but had far-advanced pulmonary tuberculosis, usually bilateral, in which collapse therapy, thoracic surgery (if it could be done), some form of antibiotic (streptomycin) or some chemotherapy (diazone, tibione) had been tried. Their prognosis was dim. A great many investigators have since said that isoniazids should be accepted in the armamentoria against pulmonary tuberculosis, but placed streptomycin and para-aminosalicylic acid (PAS) as the drugs to be tried first. In our opinion isoniazids are far superior to streptomycin and PAS.

In 1952, Ornstein, Robitzek and Selikoff[2] noted that the use of isoniazids in combination with streptomycin was more beneficial than isoniazids alone. There appeared to be a synergistic effect. The problem of proper dosage arose. At Sea View Hospital, it had been observed that good results were obtained when 10 or more mgs. per kilogram of body weight were given daily. Unfortunately, patients could not tolerate this dosage without developing signs of toxemia. However, at 8 mgs. per kilo the results were effective and there was less toxemia. Our standard dosage was then established at 8 mgs. per kilo of body weight daily. Most investigators have been using smaller doses and this may account for differences in ultimate results.

The authors have not depended on isoniazids alone, but have always, when possible, instituted collapse therapy in addition. They believed that if a case of pulmonary tuberculosis could be arrested, all available means to do so should be used. They decided that inasmuch as pneumothorax alone could be successful in controlling the disease it should still be attempted. If pneumothorax should not be feasible, then pneumoperitoneum, though a questionable form of therapy, should be used. In conjunction with this collapse therapy, isoniazids, dihydro-streptomycin and PAS are administered. The dihydro-streptomycin and PAS are used for the synergistic effect on the isoniazids and these two drugs are continued unless the patient cannot tolerate them.

We are reporting a group of patients treated in this manner, hoping to stimulate others who may have forgotten the value of collapse therapy, a process which so valued in the past now seems on the verge of becoming a lost art.

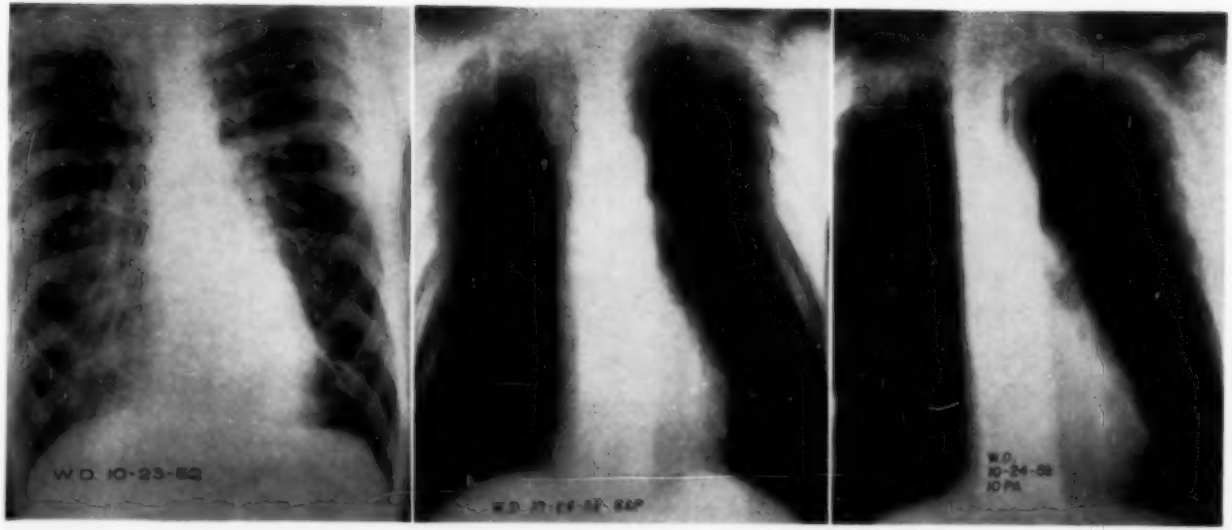

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: From x-ray films October 23, 1952 (Case I). Tuberculous lesion right lung possible cavitary formation.—*Figure 2:* Tomogram October 24, 1952 (Case I). Fig. 2 from 8 cm. A.P. film shows small cavity in the right upper lobe.—*Figure 3:* From tomogram October 24, 1952 (Case I) at 10 cm. P.A. shows large cavity right upper lobe.

Discussion

There may be a question as to what has been the important factor in the arrest of tuberculous disease of the lung. In this group of cases, one has to consider collapse therapy, isoniazids, streptomycin and PAS. The authors believe that it is more important to arrest the pulmonary disease than to be concerned with which single factor accomplished this arrest. However, each single factor should be discussed.

Collapse therapy, in the form of pneumothorax, is not a new method but one that has been with us for a great many years. Hayes and Packard's[3] survey of artificial pneumothorax as a therapeutic measure in pulmonary tuberculosis states: "It cannot be gainsaid that many lives have been saved by its use. On the other hand, it has been employed innumerable times in patients who would have doubtless recovered without it. The difference lies

TABLE I

Unsuccessful Collapse Therapy followed by Isoniazid, Streptomycin and PAS

					Pulmonary Status		Collapse Therapy	
	Name	Age	Sex	Color	Ext. of Lesion	Character of X-ray	Px.	Ppn
1.	G.R.	38	F	W	Far Adv.	Bil. exud. prod. with cavity l. l.	L. 2/16/49	2/7/51 Nov. '52
2.	E.W.	64	M	W	Far Adv.	Bil cas. pn. tbc. with bil. cavitation	L. Nov. '49	Mar. '53
3.	D.A.	50	M	W	Far Adv.	Cas. pn. tbc. *c* cavitation l. l.	L. Aug. '51	
4.	B.R.	21	M	W	Far Adv.	Bil. exud. prod. tbc. with bilateral cavitation		Jan. '52 to Apr. '54
5.	B.F.	46	F	W	Far Adv.	Cas. pn. tbc. l. l. *c* cavitation	L. Mar. '50 to Feb. '54	
6.	R.A.	61	F	W	Far Adv.	Cas. Bil. pn. tbc. *c* multiple cavitation in r. l.	R. Oct. '51 Unsuccessful	
7.	L.B.	48	M	W	Far Adv.	Bil. fibro. cas. tbc. *c* bilateral cavitation		Feb. '52
8.	R.V.	33	M	W	Far Adv.	Bil. cas. pn. tbc. *c* cavity rt. upper		Nov. '50
9.	L.J.	29	F	W	Far Adv.	Bil. cas. pn. tbc. *c* cavitation left upper lobe		July '51
10.	B.P.	50	M	W	Far Adv.	Bil. fibro prod. tbc.	L. Apr. '52	

in foretelling which patient will or will not get well by conservative treatment. In many cases pneumothorax has forestalled hemoptysis which might have led to death. It has prevented the spread of the tuberculosis to other organs, notably the larynx and the intestines."

It is our opinion that where pneumothorax cannot be done, pneumoperitoneum should be instituted. Pneumoperitoneum should be done where there is bilateral disease. The results have been considerably better when this method was combined with chemotherapy.

Streptomycin alone, or with PAS has brought about only a little more than 33 per cent spontaneous arrest of pulmonary tuberculosis, but on adding some form of collapse therapy or thoracic surgery, the results rose to 64 per cent (Ornstein and Lercher).[4]

Isoniazids in conjunction with two synergists, streptomycin and PAS, are most helpful. Under this heading arises the importance of isoniazids

TABLE I

Unsuccessful Collapse Therapy followed by Isoniazid, Streptomycin and PAS

Chemotherapy	Weight Onset	Weight Present	Sputum Onset	Sputum Conversion	Remarks
3/3/52	129	127	Pos.	6 wks.	Pnx. *c* ppn. little change. After chemotherapy, resolution occurred after 6 weeks. Last sputum Apr. '53 neg.
3/5/52-3/15/53	94	95	Pos.	*c* pnx. alone	*c* ppn. cavity closed in rt. lung but cavity l. lung still open. L. pnx. failed to close l. cavity. 1 mo. after drugs cavity closed. Last sputum Feb. '54 neg.
12/15/52 for 6 mo.	172	171	Pos.	2 wks.	*c* pnx., strept. & PAS sputum still pos. After Rimifon added sputum turned negative. Last sputum Aug. '54 neg.
3/5/52 for 6 mo. 4 mg. reduced to 1 mg. 1 kilo	211	199	Pos.	3 mos.	Collapse plus strept. & PAS failed to convert sputum. After Rimifon sputum turned neg. and has been neg. since. Last gastric Apr. '54 neg.
3/6/52 for 10 mos.	115	140	Pos.	1 mo.	Turned neg. *c* collapse and strept. and PAS, but turned pos. 2 years later. Given Rimifon and is neg. since. Last sputum June '54 neg.
3/5/52 for 3 mo. reduced from 4 mg to 2 mg. 1 kilo	97	99	Pos.	2 wks.	Collapse, strept. & PAS but cavity not closed. 1 mo. after Rimifon cavity closed. Died in psycho. ward.
3/10/52 for 10 mos.	182	199	Pos.	1 mo.	22 yr. history of tbc. *c* breakdown. Ppn. strept. & PAS failed to convert sputum. Given Rimifon sputum became negative. Last sputum June '54 neg.
3/18/52 for 1 year	127	139	Pos.	—	Negative since Rimifon. Last sputum Apr. '54 neg.
5/23/52 for 10 mos.	125	121	Pos.	2 wks.	1 mo. after Rimifon lungs showed resolution. Sputum negative after 2 weeks. Last sputum Aug. '54 neg.
3/29/54	155	155	—	—	Pnx. for control of hemoptysis. Developed cavity *c* fluid level which disappeared 2 weeks after Rimifon was given. Sputum always negative.

combined with streptomycin and PAS versus streptomycin and PAS alone. In the first publication on isoniazids in humans, (Robitzek, Selikoff and Ornstein)[1] 80 per cent of the patients were former streptomycin failures. Isoniazids succeeded in cases where streptomycin and PAS had failed. Ornstein and Lercher[4] reported that 22 patients had conversion of sputum in 26 far-advanced cases of pulmonary tuberculosis who had refused thoracic surgery or in whom thoracic surgery had failed. These were failures with streptomycin alone and converted when isoniazids were added. Therefore isoniazids appear to accomplish better results than streptomycin and PAS. There are no logical reasons for asserting that streptomycin and PAS are the first choice in the treatment of pulmonary tuberculosis.

The authors have found that the combination of collapse therapy and simultaneous use of isoniazids, streptomycin and PAS produces more rapid and permanent results. Furthermore one has not to wait to determine

TABLE II

Collapse Therapy Initiated Simultaneously with Isoniazid, Streptomycin and PAS

					Pulmonary Status		Collapse Therapy	
	Name	Age	Sex	Color	Ext. of Lesion	Character of X-ray	Px.	Ppn
1.	W.D.	54	M	W	Mod. Adv.	Cas. pn. tbc. R.U.L. *c* cavitation	Rt. 11/5/52	
2.	R.E.	23	F	W	Far Adv.	Cas. pn. tbc. *c* cavitation R.U.L.	Rt. 11/13/52	
3.	M.J.	48	M	W	Far Adv.	Bil. cas. pn. tbc. *c* bil. cavitation	L. 11/20/52	
4.	K.B.	25	F	W	Far Adv.	Cas. pn. tbc. *c* cavity rt. lung	R. 11/20/52 Unsuccessful	11/26/52
5.	G.R.	20	F	W	Mod. Adv.	Fibro. prod. tbc. L.U.L.	L. 1/8/53	
6.	M.E.	47	F	C	Far Adv.	Cas. pn. tbc. left lung	L. 1/17/53	
7.	G.A.	24	F	W	Mod. Adv.	Fibro cas. tbc. *c* cavity rt. lung	R. 2/6/53	
8.	B.H.	26	M	W	Far Adv.	Bil. cas. tbc. *c* bil. cavitation		
9.	R.E.	26	F	W	Far Adv.	Fibro, cas. tbc. rt. upper lobe	R. 4/11/53 Unsuccessful	4/18/53
10.	M.J.	25	M	W	Far Adv.	Cas. pn. tbc. *c* cavity rt. lung	R. 9/5/53	
11.	D.L.	53	M	W	Far Adv.	Cas. pn. tbc. *c* cavity rt. upper		11/21/53
12.	H.M.	39	M	W	Far Adv.	Cas. pn. tbc. *c* cavity left lung	L. 1/25/54	

whether to add further therapy after months of first trial with the isoniazids in a "wait-and-see" program.

The authors have made inquiries among students at various medical schools about how they are being educated in the treatment of pulmonary tuberculosis. We are told that streptomycin and PAS are stressed as the drugs of choice. Should streptomycin and PAS fail, then they are advised to resort to isoniazids.

SUMMARY

1. A simultaneous combination of collapse therapy (pneumothorax or pneumoperitoneum) and isoniazids 8 mgs. per kilogram, streptomycin one gram two times weekly if tolerated, and PAS 12 gms. or less if tolerated, is the best method of using isoniazids and its synergists.

2. It is not necessary to give up the art of collapse therapy which has served us so long and so well.

TABLE II

Collapse Therapy Initiated Simultaneously with Isoniazid, Streptomycin and PAS

Chemotherapy	Weight Onset	Weight Present	Sputum Onset	Sputum Conversion	Remarks
11/5/52	123	140	Pos.	1 wk.	Neg. after 1 week. Turned pos. after 1 yr. after a cold, but on drugs reconverted to neg. Pnx. only 6 mos. Last sputum Nov. 9 '54.
11/13/52	103	109	Pos.	1 wk.	Negative with 1 pos. 1/8/53, negative since. Last sputum Oct. 5 '54.
11/20/52	127	149	Pos.	8 mos.	Pt. negative since Sept. '53 in spite of open cavity in left lung. Last sputum Feb. '55.
11/52	140	154	Pos.	1 wk.	Successful pnp. with closure of cavity and neg. sputum. June '54 neg. Sputum & culture.
1/8/53	115	126	Neg.		Pnx. in left lung controlled hemoptysis. Discontinued after 10 months because of thickened pleura. Last sputum (pharyngeal smear) Nov. '54 neg.
1/17/53	110	107	Pos.	2 wks.	Turned neg. in spite of adherent upper lobe. Last sputum Aug. '54 neg.
2/6/53	105	109	Neg.		Last sputum Nov. '54 neg.
2/20/54	155	155	Pos.	2 wks.	Persistently neg. after 2 wks. of isoniazids. Failure after strept. and PAS 3 yrs. ago. Last sputum Feb. 15 '55.
4/11/53	123	132	Neg.		Pnp controlled hemoptysis. Sputum always neg.
9/5/53	171	170	Pos.	6 wks.	Negative since. Cavity closed. Last sputum Jan. '55.
11/21/53	139	152	Pos.	2 wks.	Lobectomy right upper lobe Jan. '52. Turned pos. with open cavity Oct. '53. Turned pos. 5/5/54 once, but neg. since. Last sputum Feb. '55.
1/25/54	192	200	Pos.	4 mos.	Cavity closed. Neg. after 4 mos. of therapy. Last sputum Feb. '55.

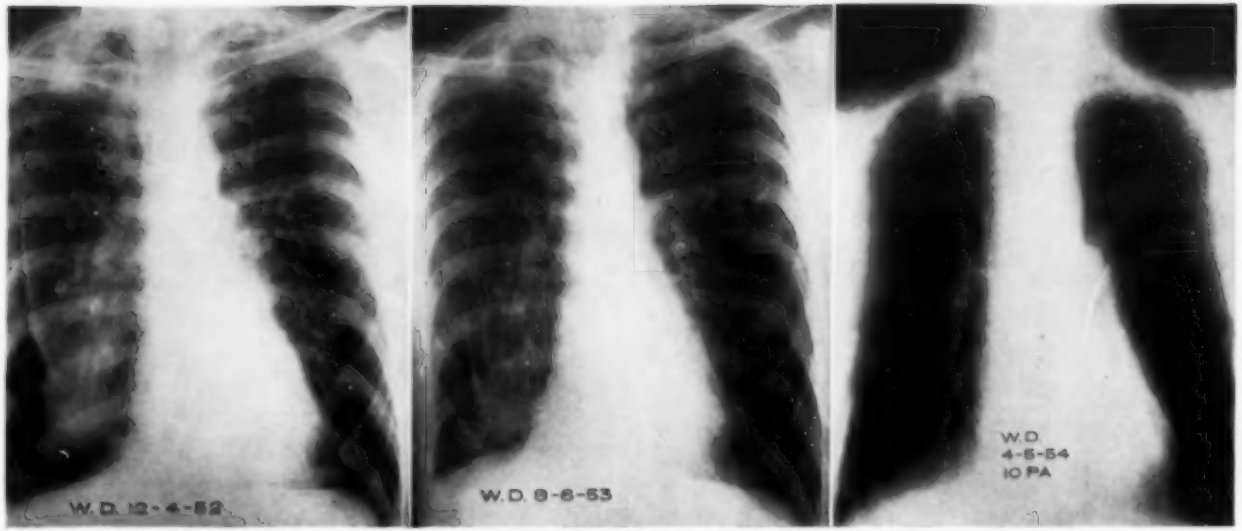

FIGURE 4 FIGURE 5 FIGURE 6

Figure 4: From x-ray film taken December 4, 1952 (Case I) showing incomplete pneumothorax. The lung was collapsed on November 5, 1952. At the same time patient was given 8 mg. of isoniazids per kilo, 1 gram of streptomycin twice weekly and 10 grams of P.A.S. daily.—*Figure 5:* From x-ray film taken August 6, 1953 (Case I). Because of the danger of some collapse of right lung pneumothorax was abandoned. —*Figure 6:* Shows 10 cm. cut P.A. April 5, 1954 compare with Fig. 3.

FIGURE 7

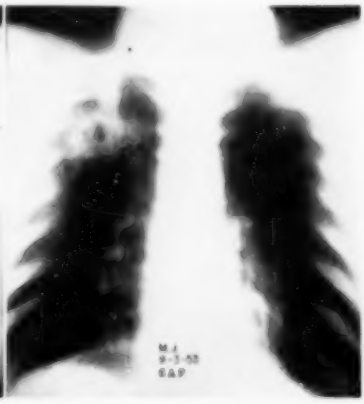

FIGURE 8

Figure 7: From x-ray film August 28, 1953 (Case II). In the right upper lobe, note inflammatory process which probably represents far-advanced caseous pneumonic tuberculosis.—*Figure 8:* September 2, 1953 (Case II). From a 6 cm. cut which shows a cavity in the right upper lobe, surrounded by a thick inflammatory wall.

FIGURE 9

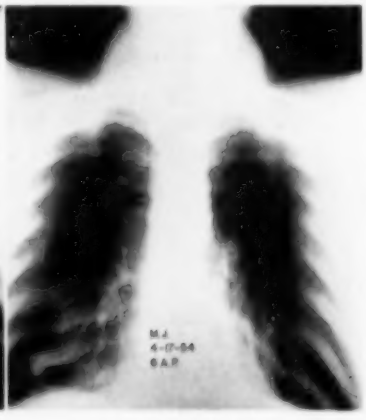

FIGURE 10

Figure 9: From 6 cm. A.P. tomographic cut November 19, 1953 (Case II). Cavity almost closed. Also visible is part of the pneumothorax.—*Figure 10:* From 6 cm. A.P. film April 17, 1954 (Case II). Pneumothorax still present. Drugs had been stopped after six months. Cavity much reduced in size.

RESUMEN

1. El mejor método para usar la isoniacida y sus sinérgicos es: una combinación simultánea de colapso (neumotórax o neumoperitoneo) e isoniacida 8 mgrs. por Kgr. de peso, estreptomicina, un gramo dos veces por semana si es tolerada y PAS 12 grs. o menos si es tolerado.

2. No es necesario abandonar el arte del colapso terapéutico que nos ha servido por tanto tiempo y tan bien.

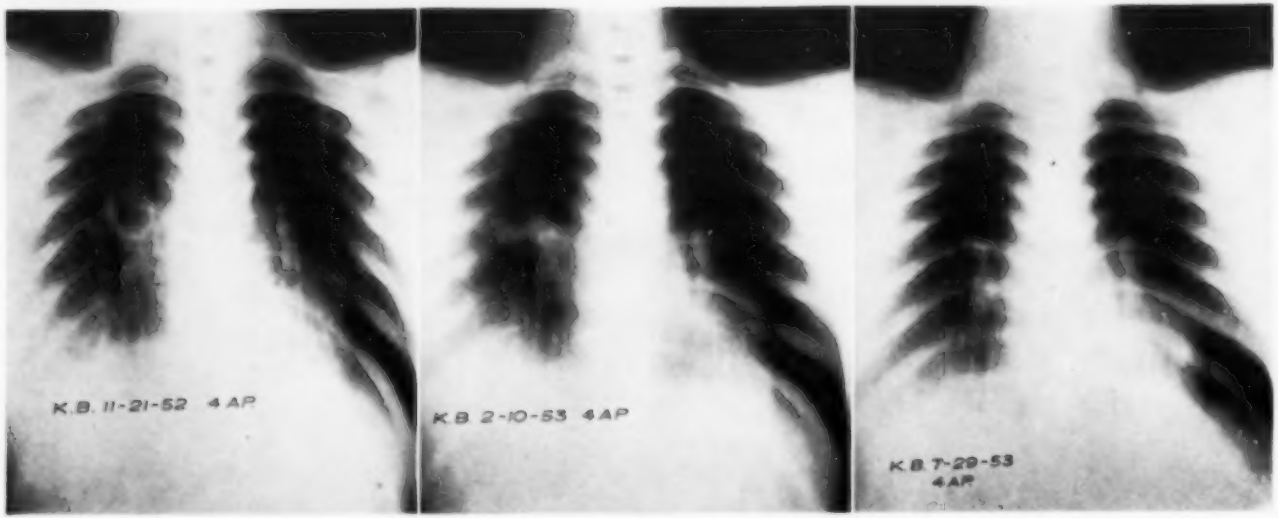

FIGURE 11 FIGURE 12 FIGURE 13

Figure 11: From 4 cm. A.P. film November 21, 1952 (Case III). Shows lesion with cavitation in the right lung with infiltration below, and some infiltration in the left lower lobe.—*Figure 12:* Pneumoperitoneum done December 26, 1952, on February 10, 1953 (Case III) 4 cm A.P. film shows disappearance of the cavity and clearing of the exudate around it.—*Figure 13:* From 4 cm. A.P. tomogram July 29, 1953 (Case III). Patient moved to a mid-western city. Pneumoperitoneum was continued but isoniazid, streptomycin and PAS had been discontinued.

FIGURE 16

FIGURE 17

FIGURE 18

Figure 16: From 8 cm. P.A. film September 26, 1953 (Case IV). Shows a highlight in the left lung. Sputum positive.—*Figure 17:* From 8 cm. P.A. film January 15, 1954 (Case IV). In spite of antibiotic therapy for an acute pneumonic condition, the tuberculous condition seemed to increase, therefore, his lung was compressed on January 25, 1954.—*Figure 18:* From 8 cm. P.A. film May 5, 1954 (Case IV). Lung looks collapsed. An irregular pneumothorax is seen but apparently it has controlled the cavitation and inflammatory process. Sputum became negative on May 3, 1954 and remains negative. Gained considerable weight.

RESUME

1. La meilleure facon d'utiliser les isoniazides et leurs agents synergiques est de les associer à la collapso thérapie (pneumothorax ou pneumopéritoine). Les doses suivantes doivent être utilisées:

8 mmgr. par kilogramme de poids corporel pour l'isoniazide;

1 gr. deux fois par semaine pour la streptomycine, si elle est tolérée;

12 gr. de PAS ou moins, s'il est toléré.

2. Il n'est pas nécessaire d'abandonner la collapsothérapie qui pendant si longtemps nous a rendu de si remarquables services.

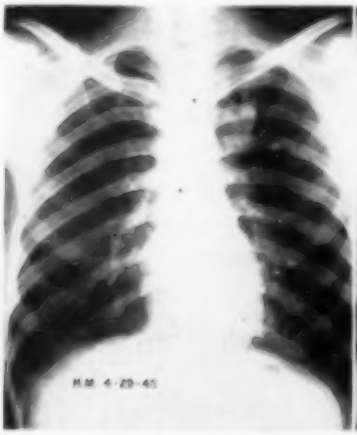

FIGURE 14

FIGURE 15

Figure 14: From x-ray film April 29, 1945 (Case IV). Apparently an end-result of a caseous pneumonic lesion in left upper lobe. Sputum was negative for tubercle bacilli.—*Figure 15:* From x-ray film September 11, 1953 (Case IV). Much improved compared to Fig. 1. Sputum negative for tubercle bacilli.

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Urinary Complications Occurring During Isoniazid Treatment

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Isoniazid as a specific agent for the treatment of pulmonary tuberculosis is being increasingly used and the tendency is for it to be given to patients who for one reason or another cannot tolerate para-aminosalicylic acid. These patients are frequently in the older age group. In addition the incidence of tuberculosis is tending towards the older individuals and drugs are administered for lengthy periods. Often they are given in homes where close observation is not as easy as in sanatoria and hospitals.

Many writers state that with the conventional dosage, toxic effects are minimal or absent. This combination of older patients and longer treatment suggests that caution is desirable before assuming that the drug is innocuous. Most accounts of results in larger series of cases mention at least some urinary symptoms connected with the use of isoniazid. This report concerns four cases where during isoniazid treatment the patients developed marked edema, with rising blood N.P.N. and in three of whom there was urinary retention as a major symptom. It is possible that the use of the drug precipitated a degree of prostatic obstruction.

Case 1: This 80 year old white male was admitted to the Middlesex County Sanatorium on November 12th, 1953. The diagnosis of pulmonary tuberculosis had been made in 1951, but he had failed to avail himself of treatment. On admission the chest x-ray film showed infiltration at the right upper zone. Tubercle bacilli were demonstrated in the sputum by concentration, culture and animal inoculation. Skin test was positive using 0.1 mgms. old tuberculin. The general clinical condition was good. Mentally he was alert and took a keen interest and active part in the life of his community. Physical examination was not remarkable. The prostate was smooth, not tender, there were no nodules and it was symmetrically enlarged to about four times normal size. On particular enquiry he stated he had never had frequency, urgency, burning on micturition, difficulty in starting micturition or other symptoms suggesting prostatic obstruction. The urine was normal on chemical and microscopic examination. The dilution and concentration power showed a specific gravity ranging from 1003 to 1027.

Treatment was commenced with streptomycin sulphate 1 gram twice a week, and isoniazid 200 mgms. daily in divided dosage (4 mgms. per kilo). In view of his age and the relatively indolent nature of the disease, which had remained radiologically unchanged for two years, he was allotted a modified rest regime being allowed up in his room for all toilet privileges and for meals. On this routine he remained symptom free, his weight started to increase and temperature remained within normal limits.

Six weeks after treatment started he reported slight swelling of the feet towards the end of the day. The clinical examination was normal. The urine was negative and blood pressure was not elevated. Fluid intake and output chart over a period of a week was satisfactory and no change in therapy was made.

On March 22, 1954 three months after the start of therapy, he again reported swelling of the feet and on examination there was pitting edema of the lower limbs to above the knees and in the sacral area. The blood N.P.N. was 36 mgms. per cent and the urine was again normal. He now complained of slight nocturnal frequency passing small quantities of urine each time. Isoniazid was stopped and there was a slight decrease of the edema. After four days it was again administered this time in error, for seven days during which time the edema increased to the previous degree. He was put on a salt free diet for a week without demonstrable effect. During the next three weeks no form of medication was given, he was kept on normal diet with

Middlesex County Sanatorium.

unrestricted fluids. Thereafter there was gradual decrease in the amount of edema and weight slowly decreased from 145 to 137 pounds but the N.P.N. increased to 50 mgms per cent and a week later to 85 mgms per cent. At this time he felt generally unwell. For the first time he complained of marked lassitude and there was a striking change in his mental well-being as he now had no interest in reading or in writing, saying that he felt too tired to do either, whereas previously and subsequently, these activities kept him continually occupied. When the N.P.N. was at its peak catheterisation yielded 300 ccs. of clear sterile residual urine and he spontaneously gave the information that since shortly after starting isoniazid he could not empty his bladder properly, that it always felt partially full after urination and that there was diminished urinary stream. One week later the N.P.N. was 49 mgms per cent and the residual urine 170 ccs. In the following weeks there was an increased urinary output, edema decreased though a trace remained around the ankles after exercise. Residual urine dropped to 75 ccs. and then to less than 10 and over this period the weekly N.P.N. readings were 46, 42, 42 mgms. per cent while the weight remained steady at 138 pounds on daily weighings. At this stage he volunteered the information that the vigour of the urinary stream was restored and the bladder felt empty after micturition. An intravenous pyelogram showed a normal pattern. Thereafter he continued symptom free until discharge in July 1954.

In this case the onset of edema and raised residual urine seemed to be related to isoniazid as they subsided when the drug was finally omitted and without other therapy. The fact that the N.P.N. continued to rise after stopping isoniazid has been noted by others and was also observed in the other cases.

Case 2: This was a 79 year old white male in whom pulmonary tuberculosis had been diagnosed by chest x-ray and bacteriological examination of the sputum at another hospital while under investigation for peptic ulcer. On admission the clinical condition was poor and he was much under weight. From the chest point of view he had minimal symptoms and examination of the lungs was within normal limits. There was slight prostatic enlargement, with a small nodule in the left lateral lobe which the consulting urologist did not consider malignant. Again on specific questioning the patient stated he had had no symptom to suggest prostatic obstruction. The urine was normal chemically and microscopically but of low specific gravity. An intravenous pyelogram done later was normal.

Treatment for radiologically proved gastric ulcer with bland diet, alkalies and Tr. belladonna m xv. three times daily, was started simultaneously with streptomycin sulphate 1 gram daily and isoniazid 300 mgms daily (6 mgms per kilo of bodyweight). Within a week of starting treatment he developed acute urinary retention. At first intermittent catheterisation and later bladder drainage with a Foley catheter failed to produce relief and transurethral resection had to be done. At operation the bladder wall showed coarse trabeculation with numbers of cellules and small diverticulae. There was little if any hypertrophy. The prostatic urethra was extremely short and the urologist felt that the obstruction symptoms were due to a narrow sclerosis of the bladder neck. A minimal resection was carried out in all quadrants about 1 gram of tissue in all being removed. When this was done the bladder neck was wide open and there was no obstruction present. The pathological examination of resected tissue showed no malignancy.

After operation he made an uneventful recovery though obstinate constipation was troublesome. This latter complaint might have been partially due to impaction of barium in the bowel. He continued to take isoniazid in the previous dosage up to the time of discharge without further incident.

Case 3: In this patient complete retention, rising N.P.N. and mental confusion occurred in a young man after eight months of treatment with isoniazid but in whom the condition subsided when the drug was withdrawn, and without other specific treatment. This was a 38 year old white male who was admitted to the sanatorium on March 4, 1953 with far advanced pulmonary tuberculosis the diagnosis being made on x-ray film and bacteriological findings. He was known to have had diabetes since the age of 22 years and diabetic control had been poor because of his lack of attention to diet and insulin. On admission his general condition and nutrition were poor. Examination of the central nervous system showed a loss of knee jerks and diminution of vibration sense in lower limbs. The blood pressure was 120/80. Urine showed a heavy cloud of albumin, red and white cells and several fine granular casts. The N.P.N. was 44 mgms per cent. The prostate felt normal to rectal palpation. The consultant ophthalmologist reported no abnormality of eyes or fundi. Diabetic diet and insulin routine were continued and treatment for tuberculosis commenced with streptomycin and para-aminosalicylic acid. He proved to be sensitive to streptomycin and unable to tolerate PAS and consequently both drugs had to be stopped. On March 12, 1953 isoniazid 300 mgms daily (5 mgms per kilo of bodyweight) was commenced at which date the N.P.N. was 37 mgms per cent. On November 9, 1953 he developed complete urinary retention. The dosage of isoniazid was reduced to

150 mgms daily and intermittent catheterisation was necessary. The blood N.P.N. was 63.5 mgms. per cent. After a week during which he was restless, agitated and confused isoniazid was stopped and continuous Foley catheter drainage instituted. The N.P.N. had risen to 93 mgms per cent. In the following weeks there was slow improvement. On December 2, 1953 N.P.N. was 130 mgms per cent but he felt better. The Foley catheter was then finally removed and normal bladder function restored. Three weeks later N.P.N. had fallen to 48 mgms per cent and there was progressive symptomatic improvement. Bladder function continued normal up to the date of death six months later in uraemic coma with terminal hypertension. Permission for post-mortem could not be obtained.

Case 4: In this case the picture was less clear cut. He was a 77 year old white male who was admitted for treatment of far advanced pulmonary tuberculosis. He was a poor witness but it appeared that in the past he had had intermittent symptoms suggesting chronic prostatic obstruction with poor urinary stream and frequency with difficulty on initiation of micturition. For some time prior to the relevant date however he had no urinary symptom.

Treatment with streptomycin and PAS was commenced but a month later PAS had to be stopped as he was unable to tolerate it. Isoniazid 300 mgms daily was then commenced but all drugs were stopped one week later because of edema from ankles to mid thigh, and he had frequency and poor urinary stream though probably these symptoms were not markedly different from previous attacks. Weight had increased six pounds in five days. N.P.N. was 60 mgms per cent one week after stopping isoniazid. Edema subsided in a month without other therapy. No real conclusion as to cause and effect could be reached but it is possible that isoniazid did precipitate some mechanism leading to marked edema and recurrence of obstructive symptoms especially in view of the spontaneous remission after it was stopped.

Discussion

In case 1 an elderly but active patient developed edema and rising N.P.N. three months after starting streptomycin and isoniazid. There was a transitory improvement when the drugs were stopped but increased edema recurred when isoniazid was inadvertently given. The only evidence to suggest prostatic involvement was the high residual urine which in conjunction with the other abnormal findings subsided when the medication was finally stopped.

In case 2 the patient developed obstruction within a week of starting treatment. The drug was continued and transurethral resection was finally necessary; but after operation he was able to continue the drug without further trouble. The appearance of the bladder at cystoscopy suggested chronic obstruction though it had not caused symptoms. It is possible that the exhibition of isoniazid was sufficient to cause acute retention but when the obstruction had been cleared at operation he could tolerate the drug.

In case 3 the patient was young and a prostatic incident would not ordinarily be expected. He, however, had obvious renal damage with grossly abnormal urine. His would be the type of case in which a diabetic neurogenic bladder might occur. This however is usually irreversible and the relative rapidity with which the condition subsided when isoniazid was stopped suggests a causal connection. The possibility that the presence of impaired renal function can increase the side effects of isoniazid has been pointed out by Latimer.

In most series reported there has been some reference to urinary disturbance. Selikoff, Ornstein and Robitzek stated a number of cases receiving 1-10 mgms/kilo of Marsilid complained of dizziness, insomnia, constipation or urinary bladder retention and suggested an autonomic

origin either para sympathetic block or sympathetic stimulation. Robitzek et al when discussing iproniazid cite delay in micturition being one of the commoner side effects and more often seen in patients over the age of 50 years and comment on the fact that isoniazid has almost complete absence of toxicity. Benson, Stefko and Roe stated that tests to detect para sympathetic blocking action or atropine like activity could not be detected in animals. In the Medical Research Council report of the clinical trials reported in the British Medical Journal mention is made of three cases of disturbance of micturition in one of whom there was considerable delay is starting micturition. Dosage in that series was 200 mgms daily of isoniazid. Sweaney and Perez noted a rise in blood urea nitrogen in almost all cases treated, which usually levelled off in a few months without interrupting treatment, and, without causing ill effects.

It would be improper to attempt to draw conclusions from four cases but the strong impression has been gained that isoniazid does have a definite effect on bladder function. These cases taken in conjunction are suggestive that there may be a danger of precipitating a condition resembling prostatic obstruction which in young and relatively healthy patients may go unnoticed, but in those with impaired renal function, or in those in whom the balance between adequate bladder function and urinary retention is precarious the effect of the drug may be to add a moment which may imperil the patient.

SUMMARY

Four cases are reported in which isoniazid appeared to cause a prostatic obstruction syndrome. It is suggested that the danger of such a complication may be greater in elderly patients or those with poor renal function.

RESUMEN

Se relatan cuatro casos en los que la isoniacida pareció causar un síndrome de obstrucción prostática. Se sugiere que el peligro de tal complicación puede ser mayor en los ancianos o en los que tienen deficiente función renal.

RESUME

L'auteur rapporte quatre observations selon lesquelles l'isoniazide semble avoir causé un syndrome de rétention d'origine prostatique. Il suppose que le danger d'une telle complication pourrait être plus sérieux chez des malades âgés ou chez ceux qui ont une fonction rénale défectueuse.

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Surgery in Aortic Disease*

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At the present time the treatment of heart disease is in a position somewhat similar to that of tuberculosis 30 years ago. At that time high caloric feeding, fresh air, and prolonged bed rest were the mainstays of treatment. The development of various forms of collapse therapy and pneumonectomy brought about a revolutionary change. This change, all for the better, was characterized primarily by a dynamic approach. During the past few years the treatment of heart disease has been augmented by chemotherapy and by surgical procedures of demonstrated usefulness. Consequently a more dynamic approach, particularly toward the problems of valvular disease, is in order and, in fact, is already in full swing.

Leaving the matter of technical procedures to the surgeons there are five main questions for which we must strive to obtain concise and specific answers:

1. How is the lesion to be detected?
2. What will be its probable course without surgical treatment?
3. What are the possible benefits from surgical treatment?
4. What are the hazards?
5. What are the criteria for the selection of patients for surgical treatment?

For the purpose of this discussion we may divide aortic lesions into two types; those in which insufficiency is the predominant lesion and those in which stenosis is the predominant lesion.

In aortic insufficiency diagnosis is primarily predicated on determination of the etiologic factor and an evaluation of the physical signs. Syphilis has been and still is, of course, the most common etiologic factor. Subacute bacterial endocarditis that has been too successfully treated is less common along with rheumatic disease. The symptoms are those of heart failure generally, especially exertional dyspnea, fatigue, and palpitation. Giddiness, fainting, and anginal syndrome are more common than in mitral disease. Paroxysmal nocturnal dyspnea, so called cardiac asthma, is especially common as a late manifestation. Exertional dyspnea and orthopnea out of proportion to cyanosis and edema are common findings. The Corrigan type pulse with the wide pulse pressure and especially the lowered diastolic pressure, the pistol shot sounds and the Duroziez's murmur are all signs of the advanced lesion. A conical type of left ventricular hypertrophy is typical along with electrocardiographic signs of left ventricular preponderance. The aortic second sound is practically always abnormal and may be diminished or absent. The typical murmur of aortic insufficiency is medium pitched and blowing in quality. It may be best heard

*Presented at the Round Table Discussion on "Surgery in Aortic Disease," Annual Meeting, American College of Chest Physicians, San Francisco, California, June 20, 1954.

at the so-called aortic area but is frequently best heard along the left border of the sternum or at the base of the ensiform cartilage. Failure to listen in these areas may result in the murmur being missed or misinterpreted. Early in the disease, of course, the only sign may be a faint, short, early diastolic murmur typical in quality and in location. In no case, however, may the intensity of the murmur be considered an index of the severity of the lesion. A small, regurgitant leak may give a loud murmur and a wide open valve a murmur of low intensity. The level of the diastolic pressure is a far better guide. If the diastolic pressure is well maintained, the regurgitation is certainly well compensated and may be of little significance.

Aortic insufficiency is a serious lesion and in most instances progresses fairly rapidly toward increasing disability. In contrast to mitral disease in which the patient may have several episodes of congestive failure with periods of relatively good function between, cases of aortic valvular disease are likely to remain cardiac invalids once failure has developed.

Although from the long-term view the number of cases of aortic insufficiency requiring surgical intervention is likely to decrease, the lesion is nevertheless of great consequence to the one that has it. Dr. Bailey's ideas with reference to relieving aortic incompetency by constricting the aortic valve area are attractive and offer promise, as also do Dr. Hufnagel's experiments with plastic valves. I somehow doubt the advisability of placing a prosthesis above the natural valve to impinge upon it.

Diagnosis of aortic stenosis is primarily based on physical signs. In younger patients the etiologic factor will almost invariably be rheumatic fever. This does not mean that history of rheumatic polyarthritis is invariably present. There may be only history of recurring tonsillitis, respiratory infection, or poor health for a number of years in childhood or adolescence. In the later years atherosclerosis is a factor and may be superimposed on rheumatic valvular disease. The symptoms are those of heart failure generally, especially breathlessness on exertion. Anginal syndrome may be a marked feature. At times the occurrence of anginal syndrome along with exertional dyspnea in a relatively young patient persisting for a long time with little or no change may be the key to the diagnosis when other signs are equivocal or lacking. Cyanosis and edema are not typical features. Rhythm disturbances are not common but when they occur are of ill omen. The heart rate is usually relatively slow and the pulse pressure narrow. There is left ventricular enlargement of rather globular type and sometimes calcification of the aortic valve can be demonstrated fluoroscopically. In the diagnosis and management of this and other heart disorders the fluoroscope is used as an instrument of physical diagnosis. Films are invaluable for the purpose of establishing a record. Electrocardiograms may show evidence of left ventricular preponderance. A systolic thrill at the aortic area with a loud, coarse murmur and absence of the aortic second sound are characteristic findings. A thrill is, of course, merely a palpable murmur and its presence has no significance other than to emphasize the loudness and the coarse vibratory quality of the murmur. It must be realized, however, that in cases having a minimal degree of

stenosis there may be no findings except a systolic murmur and indeed it must be that all cases, even those that show all the typical findings in an exaggerated degree, must have passed through a stage in which a systolic murmur was the only finding. It is not possible in these early cases to establish a diagnosis with certainty by ordinary clinical means and there will be no indication for surgical intervention. In cases of mitral stenosis requiring commissurotomy in which the presence or significance of an associated aortic stenosis cannot be established with certainty, actual measurement of the pressure gradient through the aortic valve may at times be required. Experience must accumulate as to how much diminution of pressure should be regarded as an indication for the addition of aortic commissurotomy to the operation, but it may be as little as 15 to 20 millimeters of mercury.

Aortic stenosis would appear to be one of the best tolerated of all cardiac valvular disorders. Although the lesion is progressive, it is slowly progressive and may be well tolerated during a long, active life. The progression of aortic stenosis is much slower than that of mitral stenosis and this fact indicates caution in applying to the treatment of aortic stenosis conclusions which have been reached on the basis of treatment of mitral stenosis.

There are many cases in which there is more than one defect. Insufficiency and stenosis will often be found together but rarely will there be any doubt as to which is the predominant lesion. When a case of frank aortic insufficiency presents a presystolic rumble in the mid-precordium a question of the possible presence of mitral stenosis at once arises. Differentiation is not possible on the basis of the murmurs alone. Accentuation of the first heart sound in the mitral area and of the pulmonic second sound favors the presence of mitral stenosis. The presence of an opening snap, reliably identified, may, for all practical purposes, be considered conclusive evidence of the presence of mitral stenosis. Demonstrable dilatation of the left auricle and of the pulmonary artery are valuable supporting signs. Diagnosis of the combined lesions is important. When both aortic insufficiency and mitral stenosis are present relief of the stenosis will increase the apparent aortic insufficiency and when aortic insufficiency is present, any residual or induced mitral insufficiency will have increased significance.

It is highly desirable to have a surgical procedure for the relief of aortic insufficiency which is the most rapidly progressive and destructive of the aortic lesions. The procedure must be adaptable to cases in which the operative risk is relatively great. We may expect, however, that the number of these cases is likely to decrease materially now that the treatment for syphilis has been shortened from three years to three weeks or a little more, with a corresponding decrease in expense, inconvenience, pain and danger.

It is highly desirable also to have a surgical procedure for the amelioration of aortic stenosis, particularly those cases that have both mitral stenosis and aortic stenosis and especially if both defects can be corrected at the same operation. The number of cases requiring surgery for aortic

stenosis will always be fewer than those of mitral stenosis. There is, however, no present prospect that prevention will be markedly effective and present rates of incidence may be expected to continue. In view of the fact that aortic stenosis is so slowly progressive and not incompatible with a long and useful life, operations should be considered only for those who show considerable disability. Surgeons should not be placed in the position of operating on a murmur and, furthermore, patients selected for major operative procedures should be sick enough beforehand to realize that they have been benefited by surgery. If surgery is to be used in the milder cases the operative mortality must be brought down to compare with that, for example, of subtotal gastric resection. By the same token it should become applicable to patients up to 60 years of age.

The prime indication for aortic commissurotomy is the presence of the lesion together with a significant degree of disability resulting therefrom. The younger the patient the more forceful these indications become. Contraindications include the presence of subacute bacterial endocarditis or active rheumatic fever. Age above 50 years is a hazard. Persistent myocardial insufficiency as evidenced by congestive failure, paroxysmal nocturnal dyspnea, gallop rhythm, and marked cardiomegaly which persists in spite of persistent, diligent medical treatment is also a contraindication unless the patient and surgeon are willing to assume a severe calculated risk.

The Treatment of Pulmonary Emphysema and of Diffuse Pulmonary Fibrosis with Nebulized Bronchodilators and Intermittent Positive Pressure Breathing*

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Several authors[1-9] have recently reported improvement in patients with chronic pulmonary emphysema and fibrosis after treatment with intermittent positive pressure breathing (IPPB). In practice IPPB has consisted of having the patient breathe oxygen, under positive inspiratory pressure, into which is introduced an aerosol of bronchodilator and other drugs. This is done for 15 to 20 minutes and repeated several times daily for one to two weeks or longer. Considerable importance has been attributed to IPPB. As Barach and his associates have noted,[10, 11] however, in most cases the relative importance of the various therapeutic agents has not been demonstrated. For example, the value of bronchodilator aerosols used without IPPB among patients with asthma or emphysema or both has long been known. In 1919 Huebner[12] reported the study of intermittent or continuous nebulization of bronchodilator drugs, and in 1940 Richards, Barach and Cromwell[13] stressed the clinical value of continuous inhalation technics. A much more frequently used method of administration, however, has been that in which a relatively small number of inhalations of dilator aerosol is used, as is advised by the instructions accompanying certain drugs. In contrast, both IPPB and continuous inhalation technics provide a much longer period of inhalation and, consequently, a greater dosage. It is of practical importance to the patient to establish the relative value of the several agents used in so-called IPPB therapy because of the considerable initial cost of the apparatus needed for IPPB and the requirements of maintenance thereafter. This paper presents the results of a short-term study in which the effects of IPPB alone and of bronchodilator aerosols alone were compared with the effect obtained by their combination.

The patients studied were selected on the basis of the diagnosis of chronic diffuse pulmonary emphysema, determined by their histories, results of physical examination, roentgenograms of the thorax during inspiration and expiration and results of tests for pulmonary function (table I). All patients except six had received previous treatment. Previous treatments were numerous and those used, in order of decreasing frequency, were: iodides, bronchodilators (orally or by inhalation and

*Read, in part, by Dr. Fowler at the meeting of the American College of Chest Physicians, San Francisco, California, June 17 to 20, 1954.
Section of Medicine, Section of Physiology, Mayo Clinic and Mayo Foundation. The Mayo Foundation in Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE I—Results of Tests for Pulmonary Function Before Treatment

	Oxygen by IPPB (22 patients)	Oxygen and isuprel* by IPPB (10 patients)	Oxygen and isuprel* by IPPB after oxygen by IPPB or oxygen and isuprel (33 patients)
Vital capacity per cent of predicted	58 (21-82)	56 (37-83)	54 (31-89)
Maximal breathing capacity per cent of predicted		31 (16-51)	30 (18-77)
Residual volume / Total capacity × 100		60 (48-72)	62 (50-77)
Nitrogen washout index†		8.1 (3.6-14)	9.7 (1.9-22)
Arterial oxygen saturation per cent, rest	95.2 (93-99)	96.6 (92-99)	94.9 (85-98)
Exercise change in per cent of saturation	—3.0 (+1, —12)	—3.1 (—1, —6)	—3.4 (+2, —15)

Values listed are the mean and range.
*Measurement preceding any program of treatment which included isuprel.
†Nitrogen concentration of alveolar gas delivered by maximal expiration after a 7-minute period of breathing oxygen. Analyses made automatically (nitrogen meter) and normally do not exceed 2.5 per cent.

parenterally), antibiotics, digitalis, adrenocorticotropic hormone (ACTH) or cortisone or both, allergy injections, antihistamines, cessation of smoking, breathing exercises, diuretics, phlebotomy sedatives, pneumoperitoneum, surgical resection of blebs and oxygen. Any changes reported denoted changes from the status achieved by previous treatment. Patients who smoked continued to do so throughout the short-term study.

Treatment

The following programs of treatment were conducted: (1) oxygen administered by IPPB and (2) oxygen and aerosol of isopropyl arterenol solution (isuprel*) administered by IPPB. This was given to various patients (a) without other treatment, (b) after treatment with oxygen by IPPB and (c) after treatment with oxygen and isuprel aerosol inhalations without IPPB.

Oxygen by IPPB† was given in four treatments per day of 20 minutes each. Generally 15 cm. of water pressure was used and the usual dose of isuprel was 0.5 ml. of 1:200 solution with 0.5 ml. distilled water aerosolized by a DeVilbiss no. 40 nebulizer.

For the treatments using isuprel aerosol without IPPB the same dose and nebulizer were used as with IPPB, but the nebulizer side vent was not stoppered. Oxygen at an indicated flow of about four liters per minute was used to generate the aerosol of isuprel. A Y tube on the oxygen

*The isuprel used in this study was furnished by the Winthrop-Stearns, Inc.
†The Bennett pressure breathing therapy unit and mask were used in almost all IPPB treatments except for a few cases in which the MSA ventilator was used.

tubing permitted nebulization during inspiration only. Patients were instructed to occlude the Y tube with a finger just before the beginning of inspiration. Eight to 10 natural oral inspirations were taken followed by a maximal expiration and then a slow maximal inspiration ending with a few seconds of breath holding. This was repeated twice and was alternated with about one-minute rest periods until the nebulizer was effectively emptied. The tip of the nebulizer was kept at the level of the incisor teeth and directed over the tongue. The patients were instructed not to close the lips, but to leave an airway around the nebulizer tip.

During the course of treatments, patients were questioned and examined periodically.

Results

Oxygen by IPPB.—Twenty-two men between 36 and 71 years of age (average age, 57 years) were treated. Additional diagnoses were made of chronic asthmatic bronchitis in 11 patients, pulmonary fibrosis of minor degree in three and cor pulmonale in one. Values for vital capacity and arterial oxygen saturation are listed in table I. Treatments were given for an average of 12 consecutive days. Only five of 22 patients reported any subjective improvement in dyspnea or otherwise; additional medication such as expectorants or bronchodilators had been prescribed for three of the five. Increasing dyspnea and peripheral edema developed in one patient, requiring hospitalization and other treatment. Improvements were not observed in the vital capacity or arterial oxygen saturation of patients who did not receive treatment other than oxygen by IPPB, on remeasurement at the completion of the course of treatment.

Oxygen and Isuprel by IPPB.—Forty-three patients, including two women, ranging in age from 25 to 70 years (average age, 54 years), received the combined treatment, but as part of three different programs. In addition to emphysema a diagnosis of asthmatic bronchitis was made in 13 cases, bronchiectasis in two, moderate degrees of fibrosis in three and cor pulmonale in three.

Ten men had received oxygen by IPPB in the afore-mentioned group of 22 for an average of 10.7 days without benefit. When isuprel was added for an additional 10-day period, significant symptomatic improvement was noted by seven patients.

Ten other patients received only the combined treatment of oxygen and isuprel by IPPB for an average of 13.2 consecutive days. The severity of their disability (table I) and the range in their ages were similar to others noted before. Seven reported improvement over the results obtained from previous programs of varied treatment. The improvement noted in patients of this and the preceding group included relief from dyspnea, usually beginning on the first day of treatment, followed in several days by decreased cough and volume of sputum, decreased fatigue, and varying degrees of improvement of appetite, sleep and sense of well being.

Twenty-three patients were treated with isuprel aerosol without pressure for one week and occasionally for two weeks. Eighteen reported im-

provement similar to that of patients who were given oxygen and isuprel by IPPB. Four did not improve and one required hospitalization because of progressive cardiac failure affecting the right side of the heart. Twenty-two were then given the combined treatment, including IPPB, for an additional week. The four patients who had not improved on dilator aerosols also failed to obtain relief with IPPB. Fifteen maintained the improvement achieved previously with the dilator aerosol: six of the 15 preferred the addition of IPPB in that they "opened up better" during the treatment; four preferred the aerosol without IPPB, and five had no preference. Three patients became worse during treatment with IPPB and required additional medication because of the urgency of their symptoms.

Tests for Pulmonary Function on Patients Receiving Oxygen and Isuprel by IPPB.—Various tests were conducted one or two days before treatment was started (table I) and were repeated at approximately weekly intervals (table II) at 8 to 9 a.m. without treatment since the preceding afternoon. Table II indicates that significant average changes of lung volumes or maximal breathing capacity were not observed whether or not the treatment included IPPB. However, four of the 42 patients showed significant improvement in vital capacity (VC) and maximal breathing capacity (MBC) after the morning test with no treatment since the previous day. It is of interest that these included the youngest patients studied, their ages being 25, 30, 36 and 60 years. The two youngest patients received only the combined isuprel by IPPB and improvement was noted in one week. The third patient showed improvement after one week of treatment with aerosol only and it was maintained during a second week of treatment with IPPB. This improvement was still present seven months later during which regular treatments with isuprel aerosol without IPPB had been continued. The 60-year-old patient similarly showed improvement in vital capacity and in maximal breathing capacity after one week of treatment with aerosol only, and these measurements showed further improvement during a second week of treatment with aerosol and IPPB.

TABLE II—Lung Volumes and Maximal Breathing Capacity After Treatment Expressed as Per Cent of Values Obtained Before Treatment

Treatment	Oxygen and isuprel aerosol, per cent	Oxygen and isuprel aerosol with IPPB, per cent	
	1 week	1 week	2 weeks
Maximal breathing capacity	106±5.7* (21)†	99.9±4.0 (33)	96.2±5.1 (14)
Vital capacity	98.3±2.6 (21)	98.7±3.0 (34)	98.6±3.2 (14)
Residual volume	105±3.1 (17)	100±1.9 (26)	101±1.9 (11)
Total capacity	101±1.7 (17)	100±1.3 (26)	100±1.9 (11)
Functional residual capacity	103±2.5 (17)	98.2±1.2 (26)	100±3.0 (11)

*In all instances values listed are the mean and its standard error.
†Number of patients appear in parentheses.

After eight weeks of regular aerosol therapy, however, the results of retesting showed a return to pretreatment levels, although symptomatic improvement had persisted.

In addition, the abnormal nitrogen washout indices observed before treatment showed subsequent improvement in only two of 35 patients who were restudied after one or two weeks or both.

Forty patients had arterial oxygen saturation studies before treatment. Eleven had decreased values (<94 per cent) at rest, ranging from 84 to 92 per cent. Ten of the 11 were retested and three had regained normal resting values: one after cessation of smoking and the use of breathing exercises for two weeks prior to the use of IPPB and another after one week of aerosol only; the third had received only isuprel by IPPB. Of 37 patients who had arterial oxygen saturation measurements during exercise 21 showed an abnormal decrease of more than 2 per cent prior to treatment. Five improved after some program of treatment, two after use of an aerosol dilator and three after the use of an aerosol dilator with IPPB.

Of the 37 patients exercised (step test, 15 cycles per minute on a 9-inch step) only 11 were able to complete the maximal period of five minutes. After a course of treatment only three had increased step-test tolerance, one after the use of isuprel aerosol for one week and two after the use of isuprel by IPPB for two weeks.

Immediate Effects of a Single Treatment.—Although results of the morning tests did not show average improvement, it was recognized that throughout the day the patients were experiencing the well-known effects of the dilator drugs with accompanying reduction of symptoms. Therefore, a number of additional tests were conducted to determine the immediate effects of a single treatment which, however, apparently had not persisted overnight. After the initial morning test patients were given a treatment and then retested. Table III illustrates the increased maximal breathing capacity and vital capacity which is usually observed after dilator therapy. The increased vital capacity was accompanied by a decrease of functional residual capacity and residual volume, although in such patients these measurements were still greatly abnormal. Despite these improvements, other abnormalities were essentially unchanged, including the nitrogen index, the decrease of arterial oxygen saturation during exercise and the limited tolerance to step-test exercise.

The relative day-to-day constancy of the group in their morning tests (table II) permitted a comparison of ventilatory effects of various methods of administering aerosols. It should be emphasized that an individual patient may show considerable day-to-day variations of vital capacity and maximal breathing capacity (a) when no treatment is given and (b) in response to the same method of treatment. At times these facts have not been acknowledged by those who have attributed certain degrees of change to a given treatment. Table IV shows that 31 patients showed equal average improvement of vital capacity and maximal breathing capacity whether isuprel aerosol was administered with or without IPPB. Comparison

showed that similar results also were obtained when nine patients received aerosol by IPPB, oxygen-generated aerosol, and aerosol delivered by a hand-bulb nebulizer. The same nebulizer and dosage were used for all patients. It was often necessary for one of us to assist the patients in the use of the hand bulb, either because of the fatigue induced by the prolonged squeezing necessary to nebulize the 1 ml. of solution or to insure adequate nebulization during inspiration. It should be emphasized that this comparison of hand bulb versus other methods was not intended to determine the relative practical utility, but was intended to determine whether delivery of aerosol with IPPB was more effective than that accomplished during inspirations achieved by the patient's own inspiratory muscles.

Pulmonary Fibrosis.—Five male patients from 48 to 59 years of age having marked pulmonary fibrosis of undetermined etiology also were studied. All had marked exertional dyspnea and, as shown in Table V,

TABLE III

Average Values of Various Tests Before and After a Single Aerosol Treatment

Test	Aerosol without IPPB		Aerosol with IPPB	
	Before treatment	After treatment	Before treatment	After treatment
	4 patients		4 other patients	
Vital capacity	2.38 liters	120*	2.55 liters	117*
Residual volume	3.83 liters	92*	4.37 liters	96*
Total capacity	6.18 liters	101*	7.43 liters	104*
Functional residual capacity	4.65 liters	91*	6.25 liters	94*
Maximal breathing capacity	36 liters per minute	148*	27 liters per minute	116*
Nitrogen washout index	6.3 per cent	8.3 per cent	9.5 per cent	8.5 per cent
Minute volume (O_2)	9.1 liters per minute	9.2 liters per minute	10.4 liters per minute	10.5 liters per minute
Tidal volume (O_2)	0.590 liters	0.550 liters	0.514 liters	0.582 liters
RV:TC × 100	62 per cent	56 per cent	65 per cent	60 per cent
	10 patients		7 of the same 10 patients	
Vital capacity	2.22 liters	134*	2.42 liters	115*
Maximal breathing capacity	28 liters per minute	119*	24 liters per minute	112*
Decrease arterial oxygen saturation during exercise	5.3 per cent	5.4 per cent	4.7 per cent	4.6 per cent
Exercise time	2.2 minutes	2.5 minutes	2.9 minutes	3.3 minutes

*Average value, as per cent of value before treatment.

greatly reduced values for vital and total lung capacity with a relatively small reduction of maximal breathing capacity. Only one patient showed spirographic evidence of obstructive features. Large reductions of arterial oxygen saturation were observed during exercise. Unlike the patients with emphysema these patients showed little or no change of vital or maximal breathing capacity immediately after a treatment with aerosol dilators. Combined treatment, including oxygen and isuprel by IPPB, was given for two weeks in three cases and for one week in two cases. Significant improvement was not observed, judged either by symptoms or by the tests listed in table V.

Comment

These studies confirm other reports that moderate symptomatic improvement is obtained in the majority of patients with emphysema who are treated with oxygen and isuprel by IPPB. However, in the type of patients studied and over the period used, a significant difference was not observed between effects of oxygen-generated dilator aerosols with or without IPPB. Since others have considered IPPB to be of major importance, it is appropriate to examine the available evidence.

Principal contentions for the use of IPPB in administering dilator aerosols have been that it improves alveolar aeration and that aerosols may be introduced into poorly ventilated areas of the lungs more effectively than is accomplished by inhalation technics not using positive pressure.[13-15] However, the following evidence fails to substantiate these views in a variety of respects.

Improved Aeration During IPPB.—Motley and associates[16] studied the arterial blood and expired gases of coal miners at the end of a 10-minute period of IPPB with compressed air. The average measured values showed that IPPB achieved an increased respiratory tidal and minute volume, accompanied by increased arterial pressure of oxygen (pO_2) and decreased arterial pressure of carbon dioxide (pCO_2). However, the degree of the blood changes varied considerably with the type of patients studied, being in general most marked in patients with a ratio for residual volume to total lung capacity (RV:TC) of less than 35 per cent. In patients with a ratio of residual volume to total lung capacity greater than 35 per cent, the average increase in arterial pO_2, for example, was only 6 to 7 mm. of mercury. The next question is whether the changes result from improved aeration, with more uniform ventilation to perfusion ratios of various alveoli, or whether they are attributable merely to increased total minute volume. This is indicated by the analysis of (1) the calculated ratio of dead space to tidal volume (DS:TV), and (2) the calculated alveolar-arterial pO_2 difference. The ratio of DS:TV expresses chiefly the proportion of tidal volume which ventilates the anatomic dead space and also alveoli which are overventilated relative to their perfusion and "shows the efficiency of the distribution of the ventilated gas."[17] It is normally less than 30 to 35 per cent. In Motley's patients this ratio, without IPPB, had average values from 41 to 45 per cent. However, during IPPB this ratio in all groups increased to 49 to 57 per cent.

The alveolar-arterial pO_2 difference expresses chiefly the degree to which mixed venous blood is incompletely oxygenated during passage through the lungs, either as a result of true right-to-left shunts or by passage through underventilated alveoli. At rest breathing air this difference normally is about 10 mm. of mercury or less.[18, 19] Motley and co-workers found that the average values for their patients without IPPB were increased, being 12 to 30 mm. of mercury. With IPPB, in only one group of patients without elevation of the ratio of RV:TC was a significant average reduction of 7 mm. observed, from 30 to 23 mm., and the changes were variable (S. D., 7.3 mm. of mercury). In the other three groups, including persons with increased ratio of RV:TC, either there was no change or there was an average increase above the initially abnormally high values. These data, in our opinion, do not indicate more uniform aeration with IPPB.

TABLE IV—Immediate Effects of Isopropylarterenol Hydrochloride (Isuprel) Aerosol

Test	Number of patients	Aerosol without IPPB		Aerosol with IPPB		Aerosol by hand bulb	
		Before treatment	After treatment, per cent of before treatment	Before treatment	After treatment, per cent of before treatment	Before treatment	After treatment, per cent of before treatment
Vital capacity	31	2.47±0.10 liters* (46)†	127±3.7 (46)	2.56±0.68 liters (37)	121±3.0 (37)	.....	.....
Maximal breathing capacity		30.8±2.4 liters per minute (45)	130±4.8 (45)	30.6±2.4 liters per minute (37)	126±3.9 (37)	.....	.....
Vital capacity	9	2.34±0.24 liters (9)	135±8.9 (9)	2.25±0.12 liters (9)	129±4.8 (9)	2.17±0.21 liters (9)	142±7.7 (9)
Maximal breathing capacity		24.5±3.3 liters per minute (9)	134±9.8 (9)	25.5±2.9 liters per minute (9)	129±2.4 (9)	25.2±4.1 liters per minute (9)	154±9.8 (9)

*In all instances values listed are the mean and its standard error.
†Number of observations appear in parentheses.

We have used a nitrogen meter for continuous analysis and recording of expired alveolar nitrogen concentration during a seven-minute period of breathing oxygen, before and after treatments with a dilator administered by IPPB. Although the treatment achieved improvement of vital capacity and maximal breathing capacity, the abnormally high values of the nitrogen washout index recorded before treatment were not significantly altered (table III), indicating that no major improvement of the ventilation of poorly ventilated areas was present.

We also have found that the decrease of arterial oxygen saturation occurring with exercise, which is at least in part caused by poor aeration of certain areas of the lungs, was no less after treatment with a dilator by IPPB than before (table III).

As already noted, increases of arterial pO_2 and tidal and minute volumes were noted during IPPB with air. That they were not specific for IPPB

is indicated by the increase also noted in similar patients during deeper breathing accompanying mild exercise.[3] We have observed, using continuous recording oximetry, that when some patients with emphysema voluntarily breathe more deeply and with increased abdominal-diaphragmatic excursion, the arterial oxygen saturation may increase several per cent. Others, however, show no change.

Concerning the effects of a course of treatment with a bronchodilator by IPPB several times daily for several weeks, Motley and Tomashefski[3] stated that significant alteration in the distribution factor, or poor aeration, was not observed. This also has been our experience using nitrogen washout indices as a measure of the efficiency of alveolar ventilation.

Improved Intrapulmonary Distribution of Dilator Aerosols.—The known factors that determine the delivery and deposition of aerosols are varied and complex. However, it is clear that the distribution of an aerosol need not coincide with that of gases.[20] This fact, with the present uncertainties as to the mechanisms causing underventilation of large emphysematous regions in the lungs, makes it difficult to predict whether or not IPPB would provide a more effective administration, particularly among persons who can voluntarily increase their tidal volume. Some indication as to the relative effectiveness of administration with and without IPPB is provided by a comparison of changes of vital capacity and maximal breathing capacity after administration of aerosol, as is given from reports of various authors in table VI. A consistent difference with or without IPPB is not apparent. However, Wu and associates[26] stated that administration of aerosols by IPPB to patients with chronic bronchopulmonary disease produced greater and more prolonged improvement in ventilatory function than was obtained by administration by oxygen mask. Segal and associates reported greater improvement of vital capacity in patients with bronchial asthma after administration of a dilator by IPPB than after "bronchodilator alone."[6]

A major difficulty in evaluating several of the reports which indicated inferiority of methods not using IPPB is that insufficient information is given as to what the other methods were or how they were employed. We

TABLE V—Measurements in Five Cases of Pulmonary Fibrosis Before Treatment

Test	Average (range)	Per cent of normal
Vital capacity	1.99 liters (1.65-2.45)	40 (32-45)
Total lung capacity	3.34 liters (2.7-4.0)	51 (40-63)
Maximal breathing capacity	76 liters per minute (56-101)	67 (48-89)
Nitrogen washout index	1.6 per cent (0.6-3.1)	.....
Arterial oxygen saturation, rest	95.8 per cent (93-98)	.....
Decrease with exercise	10.5 per cent (1-17)	.....

have observed numerous instances of increased benefit after proper instruction of patients in the efficient use of nebulized bronchodilators. It is probable that these patients either had not been informed of or had not followed effective procedures in the previous use of nebulizers. Therefore, several details of procedure will be discussed.

Dosage.—A number of minutes are required for the most commonly used nebulizers to discharge 0.5 to 1.0 ml. of solution. Very small fractions of the medication are delivered, for example, by five or 10 squeezes of a hand bulb,[27] and it is fatiguing to nebulize the total dose manually. This is avoided by use of a pump or of compressed oxygen to generate the aerosol. These means, however, do not have the advantages, which in some cases are of major importance, of low cost, availability and portability that a hand bulb has.

With certain IPPB machines nebulization is continued during both expiration and inspiration. When the nebulizer is used without IPPB the loss of medication nebulized during expiration can be reduced by a Y tube on the pressure line, thus permitting nebulization during inspiration only. However, the relative magnitude of the amount of medication effectively administered by IPPB with continuous nebulization or with only inspiratory nebulization is not known, since other factors, such as the breathing pattern, are also of considerable importance.

The optimal amount of bronchodilator drug to be placed in the nebulizer for a given treatment, therefore, cannot be easily set for all patients. Individual tolerance to the various drugs also varies among patients and requires modification of the dose. The practice during this study was to use 0.5 ml. of isuprel (1:200) with equal parts of water. Frequently, however, half this amount of drug produced a similar amount of symptomatic relief. If tremulousness, palpitation or sleeplessness appeared during the course of treatment the dose at each aerosol treatment was reduced 25 to 50 per cent. These unpleasant side reactions then usually disappeared. Oral use of sympathomimetic drugs has been found to increase the tendency for nebulized isuprel to produce side effects. Elimination of the oral medication was followed by relief of the unpleasant symptoms.

Significant hypertension has been considered a relative contraindication to the use of sympathomimetic bronchodilators.

Inhalation Technic.—Frequently we have seen patients who thought they were supposed to breathe through their nose while using the orally-placed nebulizer. Others have compressed the hand bulb incompletely or with improper timing, or have almost occluded the nebulizer tip with the tongue. Some held the tip in front of nearly closed lips. In addition, some patients with emphysema inspired so rapidly that is was difficult to insure delivery of aerosol during early inspiration. It is therefore necessary to provide detailed instruction by the physician or his trained attendant, and also to observe the patient's procedure after he has received instructions. When patients with emphysema are trained in the use of "abdominal" breathing exercises, proper inhalations of aerosol are facilitated. However, the patients included in our study reported herein

did not receive instruction in breathing exercises until after the period of study, except for encouragement of deep, slow and abdominal-type breathing while using IPPB.

The oral inhalation technic which we have found to be equal to administration by IPPB has been adopted from Richards and associates[13] and Dautrebande.[20] The mouth is partly open, the nebulizer tip is inserted above the lower incisor teeth and directed above the tongue. The lips are not closed but leave an airway around the nebulizer. Emphasis is placed on starting the nebulization at or just before the start of inspiration, since there is evidence that in cases of emphysema the first gas inhaled is to some extent preferentially delivered to poorly ventilated areas.[28] Eight to 10 natural breaths are followed by a maximal exhalation and a slow maximal inspiration followed by a few seconds of breath holding, intended to facilitate maximal delivery to and deposition in poorly ventilated areas. This sequence is done twice and alternated with one-minute rest periods. The latter also permit local dilator effects to develop and facilitate the distribution on succeeding inhalations and tend to avoid excessively rapid systemic absorption. Motley and his associate have reported that electrocardiographic changes attributable to dilator drugs

TABLE VI—Effect of Bronchodilators Administered by Various Methods

Condition	Number of patients	Method of administration	Medication used	Vital capacity		Maximal breathing capacity	
				Before treatment	Per cent increase	Before treatment	Per cent increase
Silicosis[5] emphysema	200	IPPB-aerosol	Vaponephrin	2.9 liters	11	55 liters per minute	22
Emphysema[4]	....	IPPB-aerosol	Varied	....	....	35 liters per minute	36
Emphysema[3]	167	IPPB-aerosol	Varied	1.5 liters	68	29 liters per minute	37
Emphysema*	31	IPPB-aerosol	Isuprel	2.6 liters	21	31 liters per minute	26
Emphysema[10]	5	Continuous-aerosol	Varied	....	....	24 liters per minute	33
Emphysema*	31	Inspiration-aerosol	Isuprel	2.5 liters	27	31 liters per minute	30
Emphysema[21]	....	6 inhalations-aerosol	"Dilator"	....	22	....	59
Asthma emphysema[22]	65	Inhalation-aerosol	Vaponephrin	....	10	....	19
Silicosis emphysema[23]	....	"Other"-aerosol	....	....	....	....	<10
Pneumoconiosis[24]	120	Inhalation-aerosol	Adrenalin	....	....	....	<10
Asthma emphysema[25]	11	Oral ingestion	Aminophylline	....	13	....	22
Asthma emphysema[25]	....	Oral agent plus aerosol	Vaponephrin	....	20+	....	30+

*This report.

were not observed when oxygen rather than compressed air was used for IPPB.[3] It is also our impression that side effects of isuprel are less with oxygen-generated aerosols than with hand-bulb delivery of similar doses. It seems possible that an increased arterial oxygen tension, such as is achieved by oxygen-generated aerosols with or without IPPB, may not only relieve hypoxemia but may also alter the circulatory effects of the bronchodilator drugs.

It is clearly recognized that the study reported here covers a relatively short period of treatment and observation. However, during this period it was possible to separate to some extent the various features of the treatment with combined oxygen and isuprel administered by IPPB. Other reports that about 70 per cent of patients with emphysema were given symptomatic relief with combined treatment were confirmed. However, a similar incidence and degree of improvement were observed with oxygen-generated aerosols without IPPB. This was noted even in patients who had previously used aerosolized dilator drugs by different and often inefficient methods.

This report obviously does not clarify the relative merits of longer periods of treatment. However, a small number of patients have been treated with various methods for periods ranging from six to 52 weeks and their responses have not led, as yet, to conclusions different from those reached as a result of the short-term study.

The inhalation of nebulized bronchodilators usually provides prompt improvement in the sensation of labored breathing and is manifested by improvement of vital and maximal breathing capacities. It has been reported recently that such treatment produces a reduction of previously elevated values of the work of breathing.[29] The partial relief of dyspnea persists for a number of hours, but is largely dissipated overnight, as is reflected by the unchanged results of tests done in the morning prior to treatment. However, despite lack of improvement in the tests used, many patients reported some persistent improvement. They were usually the patients who obtained a reduction of cough and volume of sputum. The systematic maintained use of bronchodilators appears to promote a gradual improvement in the state of bronchopulmonary hygiene. However, the persistence of dyspnea, although variably reduced, and the unchanged results of tests for pulmonary function indicate that for most patients the basic bronchopulmonary changes were not altered by any of the treatments given. Similar lack of improvement of ventilatory tests other than that demonstrable after the first treatment also has been found by Motley and Tomashefski[3] in studying a two weeks' program of treatment with IPPB for silicosis with emphysema, and Segal and associates[6] reported unchanged values for vital capacity after 30 to 60 days treatment of emphysema.

IPPB apparatus unquestionably has various therapeutic values. Its principal function is to assist inspiration and thereby provide an adequate tidal volume. We have found it beneficial in various degrees among patients with respiratory acidosis, abnormalities of the thoracic wall, and

muscular deficiencies, whose tidal volume was otherwise inadequate. During the administration of nebulized dilator drugs, IPPB likewise increases tidal volume. However, in our experience, the great majority of patients with emphysema who are still more or less ambulatory are also able to increase voluntarily their tidal volume periodically when using the aforementioned procedure of oral inhalation.

SUMMARY AND CONCLUSIONS

Twenty-two patients with chronic pulmonary emphysema were treated for two weeks with oxygen administered by intermittent positive pressure breathing (IPPB) four times daily for 20-minute periods. A bronchodilator was not used. The IPPB treatment without bronchodilators was considered unsatisfactory.

Forty-three patients received the combined treatment of isuprel aerosol and oxygen by IPPB at some time during the period they were studied. Twenty patients received the combined treatment without previous regular use of nebulized bronchodilator and 70 per cent reported definite improvement in symptoms, including decreased dyspnea, cough and volume of sputum (when present). Twenty-three patients were treated during an initial period with oxygen and isuprel aerosol without IPPB. Eighteen of these reported symptomatic improvement, an incidence similar to that obtained with the combined bronchodilator and IPPB treatment. The incidence of improvement was similar to that of other reports, in which the combined treatment was used without control studies to determine the separate effects of the features of the combined treatment. Twenty-two of the 23 patients treated with bronchodilators alone then received IPPB in combination with the bronchodilator. Three patients became worse during treatment and two were hospitalized; 15 reported continued improvement. Four of these patients preferred aerosol without IPPB, six preferred the IPPB and bronchodilator combination, feeling that it "opened them up more" and five had no preference.

Persistent objective improvement in vital capacity, maximal breathing capacity, nitrogen washout index or arterial oxygen saturation was unusual. Only four of the 42 patients, who at some time during the study received the combined treatment, had persistent improvement in vital capacity and maximal breathing capacity. Three of these patients were 25, 30 and 36 years old respectively and the fourth was 60 years of age.

Many patients who had previously used aerosol bronchodilators were found to be using them inefficiently. When they were instructed in the correct use of a nebulizer and when they followed a systematic program similar to that used with IPPB in combination with aerosol bronchodilators, the incidence of symptomatic improvement was similar to that of patients using the combined treatment during short-term treatment.

The lack of persistent change in the results obtained by various tests for pulmonary function suggests that none of these therapeutic methods alter the basic pulmonary lesion. The occasional improvement in arterial oxygen saturation, the decrease in cough and volume of sputum and the improved sense of well being suggest an improvement in the bronchial

hygiene brought about by the use of aerosol bronchodilators. The only inherent feature of IPPB that we have observed is the assurance of a relatively large tidal volume during aerosol therapy. In alert, ambulatory patients a satisfactory tidal volume can be maintained without mechanical assistance.

Five patients with pulmonary fibrosis of uncertain etiology, but with minimal evidence of bronchospasm or other obstructive features, did not improve with use of the combined treatment.

Further controlled studies are needed to demonstrate (1) the relative therapeutic effects of long-term bronchodilator treatment with and without IPPB, and (2) whether or not the intrapulmonary distribution of gases and aerosols with IPPB differs from that of similar breathing patterns achieved solely by the respiratory muscles.

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RESUMEN Y CONCLUSIONES

Se trataron 22 enfermos de enfisema pulmonar crónico durante dos semanas administrando oxígeno por inhalación a presión positivamente (IPPB) cuatro veces al día por 20 minutos cada vez. No se usó medicamento broncodilatador. El tratamiento con IPPB sin broncodilatadores, se consideró no satisfactorio.

Cuarenta y tres enfermos se trataron con la combinación de aerosol de isuprel y oxígeno por IPPB alguna vez mientras se estudiaban. Veinte recibieron el tratamiento combinado sin uso previo de broncodilatador nebulizado y 70 acusaron una mejoría definida de los síntomas incluyendo disminución de la disnea, de la tos y del volumen del esputo cuando este existía. Veintitres enfermos fueron tratados durante un período inicial con oxígeno y aerosol de isuprel sin IPPB. Dieciocho de estos, acusaron mejoría sintomática osea una incidencia similar a la obtenida con los broncodilatadores más el IPPB.

La incidencia de mejoría fué semejante aa la obtenida según otras publicaciones en que se aplicó el método combiando sin los estudios comparativos para determinar separadamente los efectos decada factor.

Veintidos de 23 enfermos tratados con sólo los broncodilatadores, después recibieron los broncodilatadores más IPPB en combinación. Tres empeoraron durante el tratamiento y dos fueron hospitalizados; 15 relataron mejoría continuada. Cuatro de estos enfermos prefirieron el aerosol sin IPPB; seis prefirieron la combinación sintiendo que ella les "abría más" y cinco no tuvieron preferencia por uno de los métodos.

La mejoría persistente, objetiva en la capacidad vital, capacidad respiratoria máxima, índice de nitrógenos eliminado, de saturación de oxígeno arterial, fueron no habituales. Sólo 4 de los 42 enfermos que alguna vez durante el estudio recibieron el tratamiento combinado tuvieron mejoría persistente de la capacidad vital y dela capacidad respiratoria máxima. Tres de estos enfermos eran deedades 25, 30 y 36 años respectivamente y el cuarto era de 60 años.

Muchos enfermos que habían usado antes aerosol de broncodilatadores, se encontró que lo habían empleado sin eficiencia. Cuando se le enseñó a corregir el uso del nebulizador y cuando siguieron un plan similar al de la combinación con IPPB la incidencia de mejoría sintomática fué similar a la queobtuvieron los que usaron la combinación a corto plazo.

La falta de cambio persistente en los resultados obtenidos por varias pruebas de función pulmonar, sugiere que ninguno de estos métodos terapéuticos altera la lesión pulmonar básica. La mejoría ocasional en la saturación del oxígeno arterial, el decrecimiento de la tos y del volumen del esputo y las mejoría del bienestar sugieren que hubo una mejoría de la higiene bronquial producida por los broncodilatadores.

La única característica propia de IPPB que hemos observado es el asegurar un mayor volumen de aire corriente durante el aerosol. En los enfermos alertas, ambulatorios, se puede obtener lo mismo sin ayuda mecánica.

Cinco enfermros con fibrosis pulmonar de etiología incierta pero con evidencia mínima de broncoespasmo o de otras características obstructivas no mejoraron con el uso del método combinado.

Se necesitan más estudios de control para demostrar (1) los efectos terapéuticos relativos del tratamiento con broncodilatadores con y sin IPPB, y (2) si la distribución intrapulmonar de los gases y los aerosoles con IPPB difiere de lo que ocurre gracias solamente a la acción de los músculos respiratorios.

RESUME

Vingt deux malades atteints d'emphysème pulmonaire chronique ont été traités pendant deux semaines par de l'oxygène administré par respiration sous pression positive intermittente, pendant une périod ede 20 minutes quatre fois par jour. Les auteurs n'ont pas utilisé de bronchodilatateurs. Le traitement par respiration sous pression positive intermittente isolé, sans bronchodilatateur n'était pos considéré comme efficace.

Trois-quarts des malades reçurent un traitement combiné d'aérosols d' "isuprel" et d'oxygène en respiration sous pression positive intermittente, pendant une certaine période de la phase d'observation. 20 malades reçurent le traitement combiné sans utilisation antérieure de bronchodilatateur nébulisé. 70% montrèrent une nette amélioration des symptômes avec diminution de la dyspnée, de la toux, et du volume de l'expectoration, quand il en existait.

23 malades furent traités pendant une phase initiale par aérosols d'oxygène et d' "isuprel," mais sans inhalation d'oxygène en pression positive. 18 d'entre eux accusèrent une amélioration des symptômes comparable à celle que l'on obtient par le traitement combiné de bronchodilatateurs et de respiration d'oxygène en pression positive. La fréquence de l'amélioration fut semblable à celle des autres observations, dans lesquelles le traitement combiné fut utilisé sans qu'on ait fait les contrôles susceptibles de déterminer les effets séparés des léments du traitement. 22 malades sur les 23 traités uniquement par bronchodilatateurs reçurent alors de l'oxygène en pression positive, associé au traitement broncho-

dilatateur. 3 malades virent leur état empirer durant le traitement, et deux furent hospitalisés. Quinze d'entre eux eurent une continuation de leur amélioration. Quatre de ces malades préférèrent les aérosols sans inhalation d'oxygène en pression positive, six préférèrent l'association inhalation et bronchodilatateur, sentant que cela "dilatait davantage leurs bronches," et cinq n'eurent aucune préférence.

La persistance objective de l'amélioration de la capacité vitale, de la capacité respiratoire maximum, de l'index de la saturation artérielle oxygénée, ne fut pas fréquente. Seulement quatre malades parmi les 42, qui à un certain stade de l'étude, reçurent le traitement combiné, eurent une amélioration persistante de la capacité vitale et de la capacité respiratoire. Trois de ces malades étaient âgés respectivement de 25,30 et 36 ans. Le dernier avait 60 ans.

On s'aperçut que beaucoup de malades qui avaient auparavant utilisé des aérosols bronchodilatateurs n'en avaient tiré aucun bénéfice. Après leur avoir appris la façon d'utiliser correctement le nébuliseur, et après qu'ils eurent suivis systématiquement un programme semblable à celui qui résulte de l'association d'inhalation d'oxygène en pression positive et d'aérosols bronchodilatateurs, la fréquence de l'amélioration fut comparable à celle que l'on obtient en utilisant le traitement combiné pendant un traitement s'étendant sur une courte période de temps.

L'absence de modification persistante dans les résultats obtenus par différents tests de la fonction pulmonaire laisse à penser qu'aucun de ces procédés thérapeutiques ne transforme la lésion pulmonaire de base. L'amélioration occasionnelle de la saturation artérielle oxygénée, la diminution de la toux et du volume de l'expectoration, et une sensation accrue de bien être semble traduire une amélioration de l'hygiène bronchique, due à l'emploi d'aérosols bronchodilatateurs. Le seul élément attribuable à l'inhalation d'oxygène en pression positive qu'observèrent les auteurs est la constatation d'une augmentation de l'air courant utilisé pendant le traitement par aérosol. En période aiguë, pour les malades ambulatoires, un volume satisfaisant d'air courant peut être maintenu sans aide mécanique.

Cinq malades atteints de fibrose pulmonaire d'étiologie indéterminée, mais avec des signes discrets de bronchospasme ou d'autres symptômes d'obstruction, ne furent pas améliorés par l'utilisation du traitement combiné.

Des contrôles ultérieurs sont nécessaires pour montrer: (1) les effets thérapeutiques relatifs du traitement bronchodilatateur avec ou sans inhalation d'oxygène en pression positive; (2) la différence qui existe entre la diffusion intrapulmonaire des gaz ou des aérosols avec inhalation d'oxygène et celle qui est uniquement due à la respiration naturelle.

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Idiopathic Dilatation of the Pulmonary Artery

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Dilatation of the pulmonary artery may occur in:

1) congenital cardiac anomalies in which the pulmonary flow is markedly increased (auricular septal defect, high defect in the ventricular septum, patent ductus arteriosus, anomalies of venous return).
2) increased pressure in the pulmonary artery (mitral stenosis, Eisenmenger complex, left heart failure, chronic diffuse lung disorders (emphysema, fibrosis), primary hypertension of the pulmonary artery).
3) combined with so-called pure pulmonary stenosis.

It appeared from the investigations of Dexter and co-workers[1] that the dilatation of the pulmonary artery in the cases under 1) was about proportional to the raised pulmonary flow. Likewise it appeared that as a rule in cases with high pressure dilatation of the pulmonary artery existed even without increased pulmonary flow. Carlotti and co-workers[2] however found no parallelism between the dilatation and the pressure or cardiac output respectively.

In the cases of greatly increased pulmonary flow and/or raised pressure in the pulmonary artery there is also as a rule dilatation of the branches of the pulmonary artery and expansile pulsations of the hilar vessels may be observed. On the other hand in cases of dilatation of the pulmonary artery in uncomplicated pulmonary stenosis the dilatation is limited to the trunk or to one of the two main branches, especially the left one. In such cases no expansile hilar pulsations are present.

Dilatation of the pulmonary artery may also occur in the absence of any other abnormality, which is subsequently called idiopathic dilatation of the pulmonary artery.

It became evident to us that with the help of the usual x-ray photograph or screening respectively of the heart it is impossible to obtain a correct impression of the diameter of the pulmonary artery. This diameter as a rule is estimated by the degree of prominence of the pulmonary arch. We compared this with the data obtained by angiocardiography. If the photographs are taken in the second oblique position, with a good technique the diameter of the pulmonary artery may be determined fairly accurately. In this way my co-workers Nieveen and Marring found the normal diameter to be 22-33 mm. I am able to show a few examples proving that definitely no parallelism exists between the prominence of the pulmonary artery in the anterior posterior photograph and the diameter determined by angiocardiographic methods (Fig. 1-3).

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The diagnosis idiopathic dilatation of the pulmonary artery can only be established by applying heart catheterization. For it is possible only by determining the pressure and the O_2 saturation in the upper vena cava, right auricle, right ventricle and pulmonary artery to exclude the above mentioned causes. A minor shunt cannot be excluded completely when no significant differences in oxygen saturation are found, but as shown by Dexter a minor shunt by itself does not cause a dilatation of the pulmonary artery. In idiopathic dilatation of the pulmonary artery the systolic pressure in the right ventricle and pulmonary artery will be equally high, the pressure in the right ventricle is not increased and the oxygen saturation in the various parts of the right heart and vessels does not show significant differences.

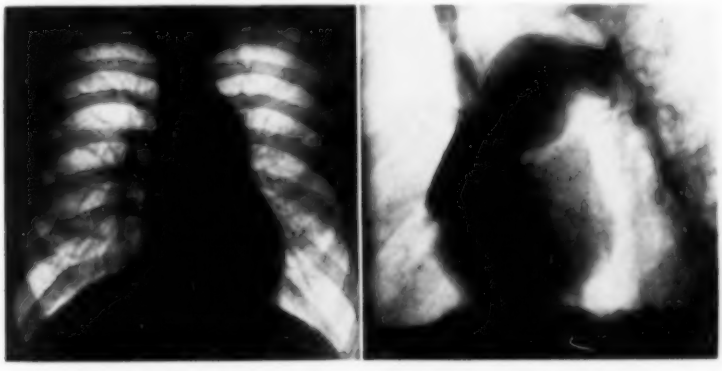

FIGURE 1A FIGURE 1B

Figure 1A: R. B., 20 years old, pure pulmonary stenosis, pressure: r. ventr. 45/0, pulm. art. 20/10.—*Figure 1B:* R. B., angiocardiogram after 2 seconds diameter pulm. artery: 62 mm.

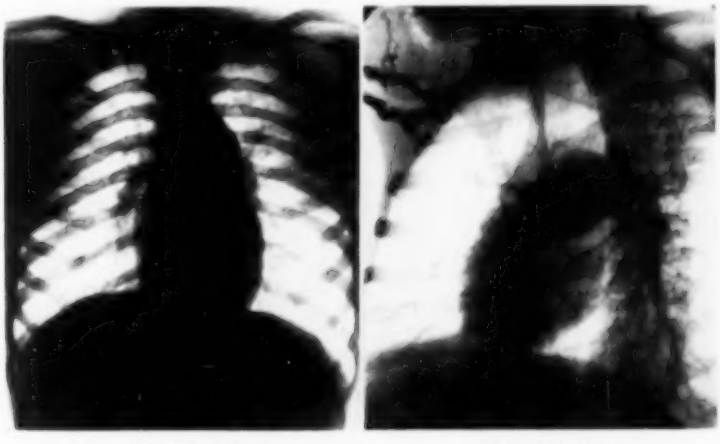

FIGURE 2A FIGURE 2B

Figure 2A: L. B., 13 years old, pure pulmonary stenosis, pressure: r. ventricle 45/0, pulm. artery 20/5.—*Figure 2B:* L. B., angiocardiogram after 2 seconds diameter pulm. art. 50 mm.

FIGURE 3A

FIGURE 3B

FIGURE 3C

Figure 3A: H., 13 years old, pure pulmonary stenosis, pressure: r. ventr. 75/0, pulm. art. 25/10.—*Figure 3B:* H., right oblique position.—*Figure 3C:* H., angiocardiogram after 3 seconds diameter pulm. art. 63 mm.

We were able to observe five such cases.

Report of Cases

Case 1: F. D., a boy, 15 years old, had no complaints and was able to play with other boys without difficulty. When he was 10 years old the school doctor found a "dysfunction" of the heart. He had never been ill. He was a well-built boy, no cyanosis, no clubbing. Blood pressure; 145/85. The pulse was regular, equal, well-filled, frequency 80. The apex beat was palpable within the midclavicular line. On percussion the heart did not seem enlarged. In the second and third intercostal space to the left of the sternum a systolic murmur was audible which did not shift towards the back, or subclavicular. The second pulmonary sound was normal. There was no other abnormality. The Wassermann reaction was negative. X-ray inspection revealed a prominent pulmonary arch was visible, lively pulsating, no hilar dance. Otherwise the heart was normal in form and size. The electrocardiogram also was normal. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery. The diameter measured 42 mm. After nine seconds some contrast was still visible adjacent to the filling of the aorta (diameter aorta 25 mm). On heart catheterization the pressure values and the O_2 saturation of the blood in the upper vena cava, right heart and pulmonary artery appeared to be normal (see table).

Case 2: H. H., a 19 year old man, had no complaint. He took part in a good deal of sport, which caused him no discomfort. When he was examined for military service a systolic murmur was found. He was a well-built young man with no cyanosis or clubbing. His blood pressure was 145/90, pulse: regular, equal, well-filled, and frequency 80. The apex beat was palpable within the midclavicular line. On percussion the heart was not enlarged. In the second left intercostal space a systolic murmur was audible, especially in the supine position, less clearly heard when standing. The second pulmonary sound was normal. Otherwise no abnormality. Circulation time 11 seconds (sulf. magn.). Wassermann reaction negative. X-ray inspection revealed a prominent pulmonary arch was visible, (fig. 5) lively pulsating, no hilar dance. The heart was normal in shape and size. The electrocardiogram was normal. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery, diameter 46 mm. On heart catheterization the pressure values and the oxygen saturation in the upper vena cava, right heart and pulmonary artery were found normal (see table).

Case 3: D. S., a 25 year old woman, complained about palpitations and breathlessness with effort when climbing stairs and cycling. She was a well-built young woman with no cyanosis or clubbing. Her blood pressure was 120/80, pulse regular, equal, well-filled and frequency 68. The apex beat was palpable on the midclavicular line. On percussion the heart was not enlarged. In the left second intercostal space a systolic murmur was audible that could not be observed beneath the clavicle or over the back. The second pulmonary sound was slightly accentuated. Wassermann reaction was negative. X-ray inspection revealed a prominent pulmonary arch was visible, no hilar dance. The heart was normal in shape and size. The electrocardiogram was normal. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery with a diameter of 49 mm. On heart catheterization normal pressure values and oxygen saturation were found in the upper vena cava, the right heart and the pulmonary artery (see table).

Case 4: K. K., a 20 year old man, had no complaint. When he was examined for military service a systolic murmur was found. He was well built and had no cyanosis, or clubbing. Blood pressure was 125/70, pulse regular, well-filled, frequency 80. The apex beat was palpable within the midclavicular line. On percussion the heart was not enlarged. In the second left intercostal space a slight murmur was sometimes audible. The second pulmonic sound was normal. Circulation time: 9 seconds (sulf. magn.). Wassermann reaction negative. On x-ray inspection a prominent pulmonary arch was visible, no hilar dance. The heart was normal in shape and size. The electrocardiogram was normal, semi vertical position of the heart. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery, diameter 40 mm. (fig. 6). On heart catheterization the pressure values and the oxygen saturation were found normal (see table).

Case 5: R. G., a 14 year old girl, was troubled by shortness of breath on exertion. She was well developed with no cyanosis, or clubbing. Blood pressure was 135/55, pulse regular, equal, frequency 90. The apex beat was palpable within the midclavicular line. On percussion the heart was not enlarged. In the second and third left intercostal space a systolic murmur was audible. Circulation time: 9 seconds (sulf. magn.). Wassermann reaction: negative. On the x-ray inspection a prominent pulmonary arch was visible (fig. 7a), on fluoroscopy there was no hilar dance. The heart was normal in shape and size. Electrocardiogram vertical position of the heart, no anomalies. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery (fig. 7b), diameter 39 mm. On heart catheterization the pressure values and the oxygen saturation of the blood were found normal (see table).

FIGURE 4

FIGURE 5

FIGURE 6

Figure 4: F. D., angiocardiogram after 3½ seconds idiopathic dilatation of the pulmonary artery.—*Figure 5:* H. H., idiopathic dilatation of the pulmonary artery.—*Figure 6:* K. K., angiocardiogram after 2 seconds idiopathic dilatation of the pulmonary artery.

All five patients showed practically the same picture: slight or no complaints. Only a systolic murmur was audible in the second left intercostal space and on the x-ray photograph a more or less prominent pulmonary arch was visible. There was no indication for a shunt, or a hypertension in the pulmonary artery.

Routier, Escalle[3] and Kaplan with co-workers[4] in some cases also were able to observe a systolic thrill. The murmur may also be absent. Kaplan[4] and co-workers emphasize that the only constant feature of the murmur is its inconstancy. We had the same experience.

The idiopathic dilatation of the pulmonary artery may be much more extensive, so that sometimes the expression pulmonary aneurysm is used. In such cases the patients as a rule have more complaints, especially about breathlessness; dilatation of the right ventricle has been found sometimes with deviation of the cardiac axis towards the right or with Wilson block. A diastolic murmur sometimes was also present (Laubry and Routier[11]). In these cases also heart failure may occur. The mild cases probably cause no complaints even later on. The strongly dilated pulmonary artery may lead to pressure phenomena, for instance in a case of Taussig[5] in which the pressure exerted on trachea and bronchi caused attacks of cyanosis and dyspnea.

The clinical picture mostly resembles that of pulmonary stenosis with dilatation of the pulmonary artery. In both cases the systolic murmur can be observed at the same localization but in cases of idiopathic dilatation the murmur does not show the typical transmittance subclavicularly and interscapularly at the back. In mild cases of pulmonary stenosis also the heart may show a normal form and size with a normal electrocardiogram (van Buchem[6]). Using heart catheterization however in idiopathic dilatation of the pulmonary artery the systolic pressure in the pulmonary artery appears to be as high as in the right ventricle. In pulmonary stenosis the systolic pressure in the pulmonary artery is lower than in the right ventricle. If the difference in pressure is not great and the pressure in the right ventricle is not increased, Green and co-workers[7] and Kaplan with colleagues[4] hold that an idiopathic dilatation of the pulmonary artery is also present. A similar case was observed by us recently.

G. H., a 15 year old girl, was only troubled by heart palpitations during extraordinary efforts. On x-ray examination an abnormality was found and therefore she was referred to us for further examination. She was slightly built with no cyanosis, or clubbing. Her blood pressure was 120/80, pulse regular, equal, well-filled, and frequency 88. The apex beat was palpable within the midclavicular line. On percussion the heart was not enlarged. In the second intercostal space to the left of the sternum a systolic murmur was audible, which was not transmitted beneath the clavicle or to the back, when standing it was less loud. The second pulmonary sound was normal. The Wassermann reaction was negative. On the x-ray examination a markedly prominent pulmonary arch was visible, lively pulsating with no hilar dance. The heart was normal in shape and size. The electrocardiogram was normal. The angiocardiogram showed a fusiform dilatation of the trunk of the pulmonary artery with a diameter of 49 mm. The diameter of the aorta was normal (30 mm.). On heart catheterization the pressure values in the right ventricle and right auricle appeared to be normal, in the pulmonary artery the systolic pressure was 5-10 mm. lower than the systolic pressure in the right ventricle: pulmonary artery 20-15/5, right ventricle 25/0 (see table).

In these cases however it is possible, as pointed out by Dexter,[8] that yet a slight pulmonary stenosis is present.

It is noteworthy that the form of the dilatation of the pulmonary artery is the same as in uncomplicated pulmonary stenosis. Likewise in both the localization is restricted to the trunk or occasionally to one of the two main branches of the pulmonary artery, but no dilatation of the peripheral branches is present, as is the rule in the cases of dilatation of the pulmonary artery with increased pressure or greatly increased pulmonary flow. Often the lungs even show only few vascular markings.

Even in cases with a moderate degree of pulmonary stenosis a marked dilatation of the pulmonary artery may be present as shown in the following:

A man, 21, was classified unfit for military service. Occasionally he had palpitations, but this complaint was not really troublesome. He was quite able to perform his work as a boatman. He had never been ill. There was no cyanosis or edema, (height 180 cm., weight 75.5 Kg.). Blood pressure was 140/75. Pulse: normal rate and rhythm. The apex beat was palpable in the midclavicular line. A systolic murmur with a duplicated first and second sound was heard in the third and fourth interspace to the left of the sternum. The second pulmonary sound was accentuated. The murmur was not transmitted to the back. The phonocardiogram did not show the spool form typical for pulmonary stenosis (fig. 8a). Urine: normal. Hemoglobin 16,3 grams, Red blood cells 5,200,000; Circulation time (magnesium sulfate) 10 seconds, vital capacity 5135 cubic centimeters (normal 4550 cubic centimeters), residual air 18 per cent. Arterial oxygen saturation: 95 per cent. pH 7.32 p CO_2 37 mm. Hg. alkali reserve: 44 per cent. A chest x-ray film (fig. 8b) showed a prominent pulmonary arch with only slight vascular markings in the lung, and no hilar dance. Electrocardiogram (fig. 8c): vertical position of the heart, no right ventricular strain. Angiocardiogram (fig. 8d): marked dilatation of the pulmonary artery (diameter 73 mm.), prolonged visibility of the pulmonary artery.

Heart catheterization (fig. 8e):

	Pressure mm Hg	Oxygen saturation
sup. vena cava	—	75
r. auricle	2	76
r. ventricle	35/0	75.5
pulm. art. trunk	20/10	77
pulm. art. periphery	7/5	98

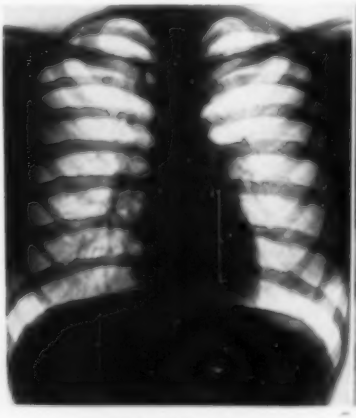

FIGURE 7A

FIGURE 7B

Figure 7A: R. G., idiopathic dilatation of the pulmonary artery.—*Figure 7B:* R. G., angiocardiogram after 2 seconds.

Cardiac output 7.3L. Calculated surface of the pulmonary ostium (Gorlin) 1.8 cm.^{2} Intracardiac injection of methylene blue did not indicate the existence of a shunt.

In this patient a marked dilatation of the trunk of the pulmonary artery was observed, while there was only a slight difference between the systolic pressure in the right ventricle and in the pulmonary artery (15 mm.). The calculated surface of the pulmonary ostium also points to the existence of only a moderate degree of stenosis. This case demonstrated that there is no correlation between the stenosis and the degree of dilatation of the pulmonary artery. It is possible that due to a dilatation of the pulmonary artery trigonoidation of the pulmonary ostium occurs, leading to a small difference in pressure between the right ventricle and the pulmonary artery. In any case the data of this patient do not support the opinion that the degree of dilatation of the pulmonary artery is determined by the size of the stenosis.

The fact therefore, that this same dilatation may also be present without pulmonary stenosis, speaks in favor of the conception that the dilatation of the pulmonary artery in pulmonary stenosis need not be caused by the pulmonary stenosis.

The explanation of the systolic murmur in these cases is thought by Chisholm[9] to be a dilatation of the pulmonary ostium. By that expansion the valves are stretched during the systole between the three fibrous noduli, localized on the wall between the insertions of the pulmonary valves.

Idiopathic dilatation of the pulmonary artery did not appear to be a frequent occurrence. Before using heart catheterization the diagnosis could not be established clinically. However a number of cases found on autopsy have been described (Oppenheimer,[10] Abbott,[13] Laubry and Routier,[11] Kourilsky[12]). One has to take into account that according to the survey of Deterling and Clagett[14] in 39 per cent of the verified cases of aneurysm of the pulmonary artery the probable cause appeared to be syphilis.

In many cases other congenital malformations were present at the same time. M. Abbott[13] found 6 cases of primary congenital dilatation on 1000 persons with congenital cardiac conditions.

NAME:		F.D	H.H.	S.D.	K.K.	R.G.	G.H.
AGE:		15 yrs.	19 yrs.	25 yrs.	20 yrs.	14 yrs.	15 yrs.
PRESSURE MM. Hg	V. CAVA SUP.	5/0	5/0	5/0	2/1	5/0	1/1
	R. ATRIUM	5/0	5/0	5/0	3/0	5/0	1/2
	R. VENTRICLE	28/0	25/0	28/0	20/0	25/0	25/0
	PULM. ART.	27/12	25/5	28/5	18/6	25/10	20-15/5
	BRACHIAL ART.	145/85	145/90	120/80	125/70	135/55	120/80
O_2 SATURATION	V. CAVA SUP.	75%	71%	76%	65%	77%	79.5%
	R. ATRIUM	74.5%	74%	74.5%	62.5%	76%	81%
	R. VENTRICLE	77%	75.5%	77%	68%	77%	82.5%
	PULM. ART.	78%	76%	77%	68%	79%	82.5%
DIAMETER TRUNK PULM. ART.		42 MM.	46 MM.	49 MM.	40 MM.	39 MM.	49 MM.
DIAMETER AORTA		26 MM.	24 MM.				30 MM.

As to the course it is probable that in mild degrees of dilatation usually no complaint will occur. At the same time cases may be found that apparently are progressive in nature, possibly leading to an aneurysm

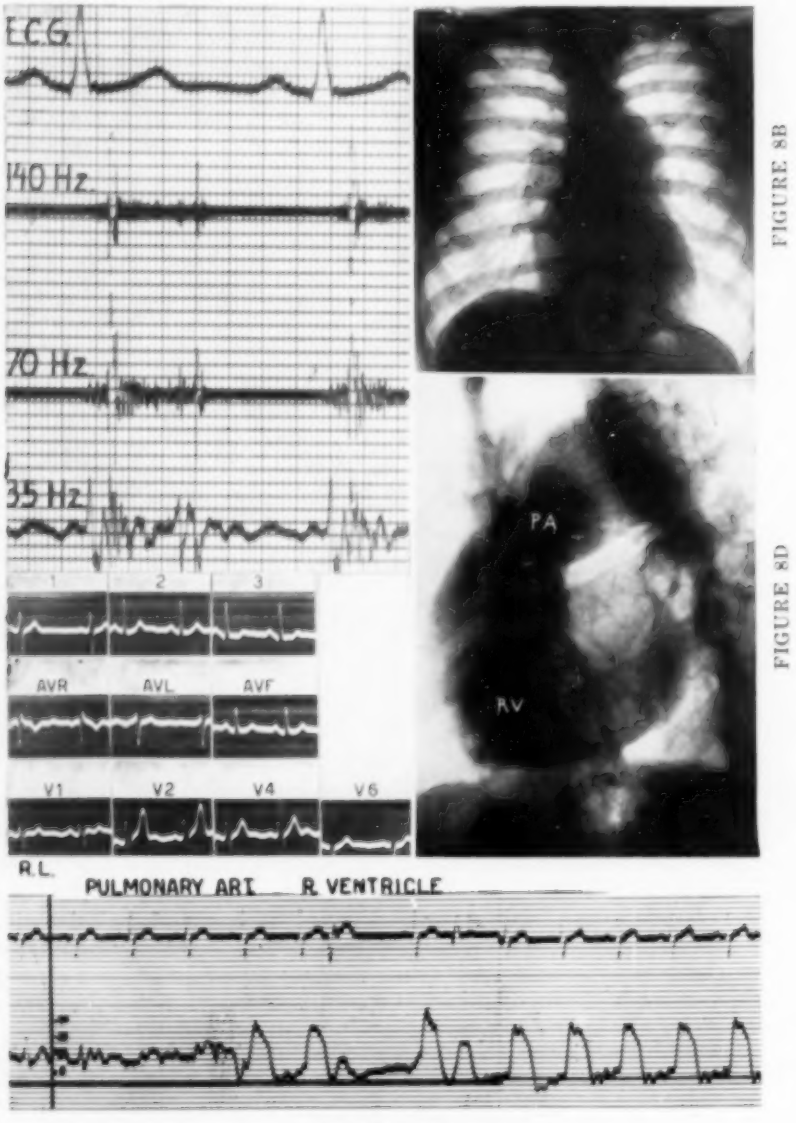

FIGURE 8A

FIGURE 8B

FIGURE 8C

FIGURE 8D

FIGURE 8E

Figure 8: R. L., slight pure pulmonary stenosis with marked dilatation of the pulmonary artery. (*A*) ECG and phonocardiogram; (*B*) prominent pulmonary arch; (*C*) ECG: vertical position of the heart; (*D*) angiocardiogram after 2 seconds diameter pulm. art. 72 mm, and (*E*) pressure curve pulmonary artery and right ventricle.

of the pulmonary artery (Deterling and Clagett[14]). One must keep in mind however that then syphilis appeared often to be the cause.

Now that we are able to establish the diagnosis with certainty during life, we might expect in future more positive data regarding eventual progression and prognosis respectively.

SUMMARY

The usual x-ray methods of examination do not give reliable information about the size of the pulmonary artery. In cases in which the pulmonary arch was only slightly prominent we found diameters of 62.5 and 63 mm. by the use of angiocardiography. Angiocardiography is necessary in order to estimate the diameter of the pulmonary artery.

Five cases of idiopathic dilatation of the pulmonary artery are presented. Heart catheterization is essential for establishing the diagnosis, for only in this way it is possible to exclude 1) congenital cardiac diseases with a marked increase in the pulmonary flow and 2) an elevated pressure in the pulmonary artery.

In idiopathic dilatation the systolic pressure in the right ventricle and the pulmonary artery are equal. The pressure in the right ventricle is not increased and the oxygen saturation in the various parts of the right heart, the pulmonary artery and the superior vena cava does not show significant differences. If the pressure in the right ventricle exceeds that in the pulmonary artery even though it is in the normal range it is still possible that slight pulmonary stenosis is present.

The clinical signs are discussed. Now that we are able to establish the diagnosis we may expect to obtain more positive information about the eventual progression and prognosis.

RESUMEN

Los métodos habituales de examen a los rayos X no dan información fidedigna acerca del tamaño de la arteria pulmonar. En casos en que el arco pulmonar arterial estaba solo ligeramente prominente encontramos diámetros de 62.5 y 63 mm. por el uso de la angiocardiografía. La angiocardiografía es necesaria para determinar el diámetro de la arteria pulmonar.

Se presentan cinco casos de dilatación idiopática de la arteria pulmonar. La cateterización cardiaca es esencial para establecer el diagnóstico porque sólo de esta manera se pueden excluir: 1) enfermedades congénitas del corazón con marcado aumento de la corriente pulmonar y 2) Una elevada presión de la arteria pulmonar.

En la dilatación idiopática pulmonar la presión sistólica en el ventrículo y en la arteria pulmonar son iguales. La presión en el ventrículo derecho no está aumentada y la saturación de oxígeno en varias partes del corazón derecho, la arteria pulmonar y la vena cava superior, no muestran diferencias significantes. Si la presión del ventrículo derecho excede la de la arteria pulmonar aunque esté dentro de lo normal, es posible que una ligera estenosis pulmonar se encuentre.

Los signos clínicos se discuten. Ahora que estamos capacitados para

establecer el diagnóstico, podemos esperar que se obtenga una información más positiva sobre la regresión eventual sobre el pronóstico.

RESUME

Les méthodes radiologiques usuelles ne donnent pas de renseignements valables concernant la dimension de l'artère pulmonaire. Dans des cas pour lesquels l'arc pulmonaire n'était que légèrement saillant, l'auteur a constaté par l'angiocardiographie des diamétres de 62.5 et 63 mm. Seule l'angiocardiographie peut permettre de déterminer le diamètre de l'artère pulmonaire.

Cinq observations de dilatations idiopathiques de l'artère pulmonaire sont rapportées. Il est indispensable pour en faire le diagnostic, de pratiquer un cathétérisme cardiaque. C'est la seule façon d'éliminer 1°) une affection cardiaque congénitale, avec une augmentation marquée du débit pulmonaire 2°) une pression élevée de 'artère pulmonaire.

Dans les cas de dilatation idiopathique, la pression systolique dans le ventricule droit est égale à celle de l'artère pulmonaire. La pression dans le ventricule droit n'est pas augmentée. Il n'y a pas de différence marquée entre la saturation oxygénée dans les differéntes parties du coeur droit, dans l'artère pulmonaire, et dans la veine cave supérieure. Si la pression du ventricule droit dépasse celle de l'artère pulmonaire, même si cette pression reste dans des chiffres normaux, il est possible qu'il y ait une légère sténose pulmonaire.

L'auteur met en discussion les signes cliniques. Etant donné la possibilité actuelle de faire un diagnostic, il pense qu'on aura plus facilement des renseignements précis au sujet de l'évolution et du pronostic.

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Respiratory Alkalosis with Especial Reference to Chest Pain

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Respiratory alkalosis may be defined as a state of altered physiochemical processes due to the excessive loss of carbon dioxide through overbreathing. Though this condition is usually referred to as the hyperventilation syndrome, respiratory alkalosis would be more accurate terminology as hyperventilation may occur as a necessary physiologic requirement without producing an alkalotic state.

That the syndrome of respiratory alkalosis (hyperventilation syndrome) is being recognized with increasing frequency is attested by the numerous reports appearing in the literature. Detailed discussions of the biochemical and clinical changes incident to overbreathing may be found in the reports of Stead and Warren,[1] Engle, Ferris and Logan[2] as well as Ferris[3] and his group. It is not within the scope of this paper to discuss all of the facets of the syndrome but rather to stress some of the clinical findings which are believed to be important in the production of symptoms.

The major biochemical change occurring in this condition is the alkalosis produced by the reduction of plasma carbonic acid through excessive loss of carbon dioxide. Thus the alkalosis is relative rather than absolute. Ferris[3] and his co-workers demonstrated that a single deep breath could reduce the carbon dioxide arterial concentration 5-7 volumes per cent and the carbon dioxide tension as much as 16 mm. of mercury. Symptoms of respiratory alkalosis therefore may develop rapidly and depending on the rate and volume of breathing they vary markedly from time to time. Indeed the symptoms of respiratory alkalosis are so varied and bizarre that a clinical pattern is difficult to recognize. With experience and awareness however, the condition becomes manifest.

As has been pointed out by Lewis[4] and others, not all cases of respiratory alkalosis are psychogenic in origin but it seems agreed that the great majority of people who hyperventilate unnecessarily do so as an expression of an emotional disturbance regardless of the presence or absence of organic disease. Thus a cardiac patient may complain of shortness of breath, pains in the chest and "poor circulation" as a result of his alkalosis rather than his heart disease. The clinician familiar with the syndrome of respiratory alkalosis will usually have little difficulty in detecting the true nature of the complaints.

The earlier articles on this subject described the acute overt attack of hyperventilation with severe symptoms, the patient being in an alarming state bordering on, if not in, tetany. While this type of case is seen

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occasionally it is the more chronic case that is seen every day in the physician's office. Many of these patients have only two or three features of the syndrome at the time of examination but nearly all will have experienced the complete syndrome at some time in the past. It is not unusual to obtain a clearcut history denoting alkalotic symptoms for many years. Two almost constant complaints in chronic respiratory alkalosis are a sense of exhaustion and ease of fatigue. On questioning these patients two points serve to distinguish their exhaustion from that of organic disease. (1) The exhaustion is greatest in the morning and tends to improve progressively during the afternoon and evening. (2) The ease of fatigue as well as the exhaustion almost always improves after a period of moderate exercise. This improvement is due to the increased production and repletion of carbon dioxide following exercise.

A disturbed sense of balance ("the blind staggers" of the Negro patient) is frequently felt by these patients. This sensation is intermittent and tends to occur in a particular environment. The acute episode is more likely to take place in close crowded spaces such as are seen in busses, theaters and elevators. Tachycardia, faintness, shortness of breath and a sense of impending disaster are often felt along with the disturbed balance.

Chest pain occurs in a large proportion of both the acute and chronic cases. This is usually, though not invariably, in the lower half of the left chest and may radiate to the neck, shoulder or to the finger tips. Often the pain will be in the scapular region and occasionally it is felt in the axilla or lower substernal regions. The pain may be intense, sharp, frequently burning in character; or a mild constant dull ache. It may occur as a fleeting twinge when lying on the side especially the left side, or bending over. When located substernally it is difficult to distinguish this distress from true angina. A useful point in differentiation is that the pain of respiratory alkalosis is often altered by holding a forced inspiration; occasionally this relieves the pain but more often it aggravates it. In almost every case moderate to severe tenderness is found on movement of the xiphoid tip.

In most of the cases of respiratory alkalosis who complain of chest pain, some alteration of the diaphragm may be found. With fluoroscopy it is common to see a large accumulation of air in the stomach or splenic flexure, with considerable elevation of the left leaf of the diaphragm. This leaf lags on downward excursion either with or without the air bubble. The most extreme examples are seen in cases of paralysis of the left phrenic nerve and the symptoms of indigestion, chest pain and shortness of breath following such paralysis have long been recognized. While everyone swallows air to some extent, with an atonic left diaphragm, hypomotility of the stomach with mild pylorospasm delay the air in the stomach. Tenderness over the interspaces in the region of the precordium is an almost constant finding. Stewart Wolf[5] reported distinct changes in the behavior of the diaphragm under conditions of stress. Decreased motility of the diaphragm has also been noted during hyperventilation.[6]

The diaphragm is attached anteriorly to the xiphoid and fascia of the transverse abdominal muscles. Laterally it arises from the costal cartilages of the lower six ribs and the bony portions of the last three ribs. Posteriorly the attachments are to the three upper lumbar vertebrae.

Thus the location, radiation and type of pain along with the tenderness over the rib and xiphoid attachments as well as the frequent findings of the elevation and lag on fluoroscopy all seem to point to the diaphragm as the chief source of pain in respiratory alkalosis. (These findings are commonly seen in the early pneumoperitoneum patient whose diaphragm is beginning to rise.) It may be assumed that the pain originates in the tendinous insertions through prolonged stretching and atony of the diaphragm. A similar type of pain and soreness is produced in the tendon attachments of the skull in tension headaches.

Though not all patients with respiratory alkalosis exhibit pain in the chest it is possible that some patients may hyperventilate as a direct result of the upward dislocation and stretching of the left diaphragm through distention of the gastric fundus or the splenix flexure of the colon. In many of these cases the upward displacement of the diaphragm is enough to compress the left lung to a degree sufficient to alter the normal respiratory reflexes and produce overbreathing. Stretching and atony of the diaphragm may account for the sensations of air hunger so often felt by these patients.

The diaphragm rises in the reclining position through the pressure of the abdominal wall and viscera; it is not unusual to find the tympanitic note of a large gastric air bubble well above the fourth anterior rib in this position. With the increased stretching of the diaphragm incident to its rise in the reclining position, undoubtedly overbreathing occurs during sleep, and so the symptoms tend to be more prominent in the morning. Often hyperventilation is the presenting symptom in cases of diaphragmatic hernia, the symptoms being relieved when the hernial sac is empty.

Treatment

Though much has been written about this syndrome very little has been said about treatment. Most authors have stressed paper bag rebreathing, reassurance of the patient by reproduction of symptoms and psychotherapy. Calcium gluconate has been condemned as having no rational place in treatment. Very rarely one will see mention of acidulation with ammonium chloride or ammonium nitrate. The fact is no trustworthy plan of relief has been found and the physician must largely improvise his own regime. A simple non-technical explanation of the condition after a thorough, unhurried history and physical examination is a necessity. Routine laboratory work and, if the patient is heart-conscious, an electrocardiogram present negative evidence to strengthen your diagnosis. To the skeptical patient reproduction of symptoms through forced overbreathing is at times convincing but all too frequently acute symptoms occur which are unlike the complaints and serve to undermine rather than increase confidence. The demonstration of a large gastric air bubble on a chest

x-ray or at the time of fluoroscopy is very convincing evidence. The fact that a positive diagnosis rather than "just nerves" has been made affords the anxious patient a great deal of comfort and relief. Though no defect in calcium metabolism has been attributed to respiratory alkalosis, parenteral calcium gluconate in my experience often gives dramatic relief for several days. Calcium salts are probably effective solely through their ability to produce both smooth and striated muscle relaxation thereby reducing the spastic elements which are so prominent in the production of symptoms.

Ammonium chloride given to tolerance (usually about 5 grams a day) affords relief to some. Mild sedation is of considerable help even in the exhausted cases. Avoidance of sodium bicarbonate, fruit juices and other alkalinizing agents is strongly recommended but other dietary restrictions seem unnecessary. Holding a deep breath to the breaking point is many times effective in breaking the symptom cycle particularly in crowded places. Dizziness, numbness and tingling are effectively controlled by rebreathing in a paper bag to dyspnea or by inhaling the fumes of a small block of dry ice (solidified carbon dioxide).

Perhaps the one most effective item in treatment is the institution of regular outdoor exercise in the form of long walks. This is difficult treatment to enforce because of the ease of fatigue and chronic exhaustion. It is explained that exercise releases tension, replenishes the carbon dioxide and strengthens the diaphragm. With these strong arguments most of these sufferers will at least take a few trial walks. It is gratifying to both the patient and physician to see what a few days of long walks will accomplish in relief of symptoms.

Case Reports

Case 1: A 65 year old widow was seen March 1940 with a severe acute anterior myocardial infarction. Following a stormy illness during which she had pulmonary edema and congestive failure she returned to a normal though somewhat restricted life. Her blood pressure was stabilized at 150/110 and she had no return of failure at any time. She had few complaints until January 1952 at which time she developed a constant dull aching over the precordium not related to exertion. The pain was worse at night and was partially relieved by sleeping on several pillows. Nocturnal leg cramps, smothering sensations, numbness and tingling in the extremities and tachycardia occurred almost every night. In the mornings she felt thoroughly exhausted and was worn out after cooking breakfast. By 4 P.M. she felt perfectly well. Examination revealed no new findings other than xiphoid tenderness and an elevated, atonic left diaphragm, with marked lagging of the downward excursion on fluoroscopy. Heart size and electrocardiogram were unchanged. Gastro-intestinal series revealed a large hiatus hernia which reduced promptly in the erect posture. She was given ammonium chloride, 1 gram three times daily and told to elevate the head of her bed with eight inch blocks. Rebreathing in a paper bag on arising was advised if she felt faint. On this simple plan she rapidly improved and is at present asymptomatic, except for an occasional mild nocturnal pain.

This patient presented a clear cut example of respiratory alkalosis directly due to a disturbance in diaphragmatic function.

Case 2: A 35 year old female office worker was found to have minimal exudative tuberculosis in the left upper lung field in June of 1940. She spent 11 months in a sanatarium on a modified rest regime. During this time a left phrenic crush was performed resulting in a rise of the left diaphragm to the fourth anterior rib level where it has remained since. She was discharged as arrested and gradually returned during the course of a year to a normal life. Since 1945 chest x-ray films have been consistently unchanged and numerous sputum studies have been reported negative. Her general health has been excellent. However, she has complained of a dull aching

pain over the precordium referred to the left scapular area, a sense of breathlessness and marked exhaustion with ease of fatigue, particularly in the morning hours. Numbness and tingling in the extremities, tachycardia and drawing sensations were almost daily symptoms. All of her complaints were dated from the time of the left phrenic crush. Except for obvious hyperventilation of the rapid shallow type, xiphoid tenderness, and evidence of a huge gastric air bubble, physical examination was negative. On fluoroscopy the left dome of the diaphragm was at the level of the fourth anterior rib and was immobile. A grapefruit sized accumulation of air was present in the gastric fundus. Barium swallow revealed mild pylorospasm with hypomotility of the stomach.

Ammonium chloride and phenobarbital-belladonna mixture gave only slight relief. Intramuscular calcium gluconate was temporarily effective. She was instructed to take a two mile walk on her way to work every morning. After a few days improvement was marked, particularly as to fatigue and dizziness.

This patient was offered a plastic repair of the diaphragm but preferred to remain on a medical regime.

Unquestionably improvement occurred as a result of carbon dioxide repletion following exercise.

Case 3: A 28 year old veteran was seen in February 1947 with a two year history of of frequent attacks consisting of nervousness, fatigue, dizziness, palpitation, polyuria and stabbing over the precordium. The pain radiated to the left elbow and cut off his breath. All symptoms increased while ridng to work on the bus. By nightfall he usually felt improved. A peptic ulcer was treated successfully while in the army in 1944. Medical and psychiatric treatment were given in a Veterans Administration Hospital with no improvement.

Examination revealed a tense anxious male with frequent sighing respirations. The xiphoid tip was exquisitely tender and tenderness was present over the precordial interspace. Evidences of a large gastric air bubble were apparent. A gastro-intestinal series showed a duodenal deformity apparently due to an old healed ulcer. Moderate pylorospasm and hypomotility of the stomach were also noted. The left diaphragm was elevated and moved sluggishly.

Phenobarbital-belladonna mixture relieved the bloating somewhat but the other symptoms remained. Coated tablets of ammonium chloride, 3 grams each day were prescribed and long walks were advised. Within a week all symptoms and findings had disappeared and he "felt wonderful." Aside from minor relapses he has had little trouble since and "walks off" his alkalosis without medication.

This patient was discouraged by his failure to improve on previous medical and psychiatric care. Perhaps the strong reassurance given was a factor but improvement was sustained only after regular exercises.

SUMMARY AND CONCLUSION

Chronic respiratory alkalosis is a common syndrome with varied and bizarre symptoms.

Physical findings as well as fluoroscopic studies indicate abnormal diaphragmatic function as a cause of pain and hyperventilation.

Reassurance, acidulation, mild sedation and, especially, regular exercises form the main treatment.

RESUMEN

La lacalosis respiratoria crónica es un síndrome común con síntomas variados y bizarros.

Los hallazgos físicos así como los estudios fluoroscópicos indican una función diafragmática anormal como causa de dolor y de hiperventilación. Son el tramamiento principal la recuperación de la confian za, la acidificación, sedación moderada y especialmente los ejercicios con regularidad.

RESUME

L'alcalose des affections pulmonaires chroniques est un syndrome banal dont les signes sont variés et curieux.

L'examen physique et l'étude à l'écran radioscopique montrent que la

fonction diaphragmatique est anormale et provoque douleurs et hyperventilation.

Le traitement essentiel consiste en reprise de la confiance, acidification, traitement sédatif doux et particulièrement exercices réguliers.

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Does Pulmonary Tuberculosis Continue to be a Chronic Problem?*

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There appears to be a growing belief—and not within lay minds only—that tuberculosis is no longer a problem to be concerned with on the community level and also that the diagnosis of active tuberculosis for the individual patient no longer carries the implications of long term disability and economic dependency as in the past. Do the available facts warrant such an optimistic view? In regard to the present magnitude of the tuberculosis problem, there has been much publicity given to the marked drop in the mortality rate in this country from the 1900 figures of approximately 200 per 100,000 population to approximately 12 per 100,000 at present. It is this evidence, primarily, which has led to the conclusion that tuberculosis has gone the way of typhoid, diphtheria and smallpox. However, as Edwards and Drolet have pointed out, "the death rate from tuberculosis is a limited and inadequate index of the problems of disease in the community." Morbidity statistics indicate that the number of new cases reported yearly has fallen little and that with patients being kept alive, who formerly would have died, the total number of accumulated cases in need of supervision is greater now than in previous years. It is the living patients who make up the tuberculosis problem, both as to their treatment needs and the threat they present to perpetuation of the disease. Hinshaw put it very succinctly in a recent talk, that "dead men tell no tales and also do not spread bacilli." Most recent figures indicate that there are approximately 1,200,000 in the United States with tuberculosis in some form; 400,000 are considered active, with 150,000 of these unknown. The active cases present a sizable reservoir for spread of infections and the inactive ones a potential group for endogenous reactivation.

The continuing high morbidity some have considered to be due to increasing population, improved case finding and better reporting, rather than to a true high rate of disease. However, the case rate (number of cases per 100,000 population) curve has remained practically constant for the past 20 years. Improved case finding undoubtedly has played some role in maintaining the morbidity figures in recent years, although by far the majority of cases, unfortunately, still are not brought to light by survey work or contact investigation but through examination of people with advanced disease who visit physicians' offices, clinics or hospitals, because of symptoms. The factor of better reporting of cases is debatable.

Studies on the incidence of infection which would be the truest measure of frequency of contact of the populus with tubercle bacilli have not been

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done on an adequate scale to reach a definite conclusion. However, skin testing of selected groups, such as school children, nurses and college students, indicate a definite lessening in the incidence of infection. For example, at the University of Pennsylvania in 1931, 51 per cent of the students entering were positive reactors and in 1953, only 14 per cent. In the past 20 years, the number of positives have dropped from 33 per cent to 11 per cent at the University of Minnesota. Nevertheless, it has been estimated that there are approximately still some 50 to 60 million positive reactors without evidence of present disease in the United States—another sizable potential group of endogenous reactivators. In addition to our own reservoir, it has been pointed out that tuberculosis is now the leading disease and the cause of millions of deaths yearly in other portions of the world where our men and women may be sent.

In a recent speech, Dr. J. H. Harley Williams, of England, termed it today's most important tropical disease. It has been estimated that approximately 10 per cent of the population in the Orient are walking around with infectious lesions. The outside world cannot be neglected as a factor in our total tuberculosis picture in the United States. The goal of eradication of tuberculosis in this country could be delayed greatly and it is not inconceivable that there might be an actual increase in disease amongst us if there were a marked alteration in our standard of living, too rapid a withdrawal of segregation and treatment facilities, or a diminution in efforts to ferret out the unknown cases in our midst. Although there may be some differences of opinion, in regard to the emphasis which should be placed upon various elements in the tuberculosis control program, there is complete accord with the view that there must be no slackening of control measures.

In our approach to gain victory over tuberculosis within the individual patient, however, there is less agreement. We have experienced a revolution in the treatment of this disease initiated by the advent of antimicrobial agents and improved surgical techniques. This revolution is far from ended, with many unanswered questions and varying views keeping the cauldron boiling. Uncertainty exists in regard to the best combination of antimicrobials and how long they should be given, as to the significance of isoniazid resistance, the role of minor collapse procedures, over whether closed lesions should be resected etc.; but the most inciting questions of all are those directed at the long established principles of non-specific treatment aimed at favorably influencing the host parasite relationship.

Originally, the new agents, along with surgical improvements were merely considered as adjuncts to the time honored and empirically proved regimen embracing physical rest, peace of mind, adequate diet and a gradual resumption of the responsibilities of a normal life program after stabilization of disease. The majority still appear to hold that this basic framework should be incorporated in the modern therapy program, voicing the opinion that until long term results of management with antibiotics, plus rest, are known, it would be unwise to discard those measures directed at bolstering of native resistance, consolidation of healing gains

and prevention of relapse. The proponents for retaining rest as a basis for treatment point to the more rapid reaching of target point in a large proportion of cases with consequent earlier ambulation as a sufficient stride towards lessening the chronicity of tuberculosis without providing a hazard to the patient. The members of this group emphasize we must recognize that the present antimicrobials are not bactericidal, only bacteriostatic, and as long as viable organisms may be retained within the body (and surgery does not guarantee their removal) the factors which are felt to play a role in influencing native resistance cannot be neglected. The fact that relapses are still occurring, although so far in small numbers, despite antimicrobial therapy, they feel is further justification to utilize all of the treatment aids at our command.

However, there are others who propose that bed rest can be dispensed with long before the target point is reached without ill effects. They consider the antimicrobials to be the basic requirement in the treatment program and question the role that rest plays in bringing about the rapid subsidence of symptoms, x-ray clearing and bacteriological conversion in types of disease which were rarely known to respond in this fashion with rest, relaxation and diet alone. They point out that even prior to the days of streptomycin there were some who questioned the significance of bed rest, especially its strict application. Recalcitrant exceptions who did well, despite complete disregard for instructions were familiar to all as were the other unfortunate exceptions, the cooperative patients who displayed a downhill course despite a vegetable-like existence. Such exceptions did not negate the fact that the majority of patients on rest did do well and the majority who flaunted the rest program did poorly. However, Bray and others reported the use of liberalized rest programs deliberately or because of limited personnel, with successful arrest of disease comparable to results obtained with strict bed rest. As to the argument, that lengthy rest programs prevent relapse, statistical reports such as those of Mitchell and De Fries cast doubt on the importance of rest in avoiding breakdowns, although there are so many variables involved, especially after the patient leaves the sanatorium, that an interpretation of such data is difficult.

In recent years, reports from Pittsburgh, New York, Cleveland, Chicago and Detroit suggest good results on early ambulation programs with antimicrobial agents. These programs were initiated largely because of poor bed situations or in patients who would not accept sanatorium placement. However, deliberate early ambulation efforts in the sanatorium are being tried. There is a wide variation practiced from only slight modification of the strict bed rest regimen to the most extreme example as reported by Dressler and Middlebrook who are getting all patients up on graded physical activity immediately acute symptoms have subsided without regard to x-ray or bacteriological status. Clearly, it is too soon to be able to come to conclusions concerning these medical regimens slighting the role of rest.

As to the role of surgery, when it is added to the drug program, cavity

closure or elimination and sputum conversion are obtained more rapidly and in a higher percentage of cases. The general view is that if medical management has not obtained the desired results within six to nine months, that surgical aid should be given, if at all possible. The trend still favors resections. The enthusiasm, however, for removing stable target point foci dwindled somewhat as it was discovered that a high percentage of resected specimens were either negative or revealed organisms which could not be grown or produce disease in animals. Late reports with improved techniques, such as outlined by Hobby, suggests that a high proportion of these organisms may well be virulent. There have been some reports on short term follow-up of resected and non-resected target point cases suggesting no significant difference in relapse rate of the two groups. Others do not support this view and here, too, only time and observation will give the answer. However, if long term drug therapy does prove effective in preventing relapse of target point cases, the length of treatment for a high percentage of patients will be further reduced through avoidance of surgery.

In the matter of post-sanatorium rehabilitation of arrested and inactive cases, there is also a tendency to question the need for cautious redirection of patients into pursuits which would be less demanding than their original vocations as a prophylaxis against breakdown. It is being expressed more frequently that most patients can be returned safely to their previous occupations if physically able to do so under the protection of long term drug therapy. Here, too, is a promise for reducing the chronicity of the tuberculous if the need for long drawn out retraining programs can be dispensed with.

Mention should be made, before closing, that unfortunately a small proportion of patients have very long standing extensive disease at the time of detection which responds poorly to chemotherapy. If definitive surgery is not possible the chronicity of tuberculosis for this group is not altered. Then there is another small section of patients for whom modern treatment has meant an actual increase in chronicity of disease. These are the advanced cases who would have expired in previous years but who, with antimicrobials, are kept alive as long term custodial cases.

To sum up, it is evident that despite the downward course of tuberculosis, in the United States, this disease still presents an epidemiological problem of considerable magnitude and any slackening of control measures would be hazardous. As far as the individual patient with active tuberculosis is concerned, treatment is still of relatively long duration with no rapid treatment program as for lues, on the horizon, as yet. Nevertheless, there is a definite trend towards lessening the duration of disability greatly with a growing acceptance of the thesis that prolonged physical and mental inactivity may not be essential. Clearly, the validity of this approach must be tested by time. Early enthusiasms may well prove unfounded as late relapses occur. A large proportion of phthisiologists believe that we should be content with the comparative earlier return of patients to normal life programs now obtained under treatment embrac-

ing both the antimicrobials and the previous principles of rest therapy. However, the prospects of a much more rapid resumption of a normal existence are so exciting to both patient and physician that a thorough testing of increasingly early ambulation of selected patients, under careful supervision, definitely appears warranted, especially in view of the favorable evidence in this direction to date.

SUMMARY

1. Despite the widespread belief fostered by the marked decline in the tuberculosis mortality rate that this disease has been conquered in this country, tuberculosis still presents an epidemiological problem of considerable magnitude in the United States:
   (a) Morbidity statistics do not parallel the precipitous drop in the tuberculosis mortality rate.
   (b) With the new cases reported falling off little, and many cases being saved, who in previous years would have died, the total number of known cases in the community representing potential source of reactivation or spread, is actually greater than in previous years.
   (c) Although the incidence of infection has diminished in the United States, as revealed by skin testing of selected groups, it is estimated that there are still some 50 to 60 million tuberculin reactors who offer a sizeable potential for endogenous disease.
   (d) Tuberculosis is still the leading disease problem in many other portions of the world, notably the Orient, and the United States is not completely isolated from these outside sources of infection.
   (e) Slackening of accepted control measures could conceivably result in an increase in the incidence of tuberculosis in this country.
2. In the realm of medical and surgical management of the individual patient with tuberculosis, treatment is still of relatively long duration with no rapid method as for lues.
   (a) For a small segment of patients with extensive disease, who would have died in previous years, but now are saved by antimicrobial therapy, to remain as custodial cases, there is still a definite problem of chronicity.
   (b) However, for the large majority of patients, treatment, embracing the antimicrobials and surgery, is returning them to active life programs in a much shorter period of time than in the past.
   (c) The trend is growing to question the importance of rest and the need for a cautious resumption of normal pursuits in the arrest of disease and prevention of relapse.
   (d) Only long term follow-up studies can determine the validity of this approach but the prospects of a rapid return to a normal existence are so exciting to both patient and physician that a thorough test of increasingly early ambulation definitely appears warranted, especially in view of the favorable evidence in this direction to date.

SUMARIO

1. A pesar de la extendida creencia, alimentada por la marcada declinación en la curva de mortalidad por tuberculosis, de que esta enfermedad ha sido conquistada en este país, la tuberculosis todavía representa un problema epidemiológico de considerable magnitud en los Estados Unidos:

a) Las estadísticas de morbilidad no paralelan le caída estrepitosa de la curva de mortalidad por tuberculosis.

b) Con los casos nuevos reportados, que han disminuído poco y muchos casos que han sido salvados, de los que en años previos hubieran muerto, el número total de casos conocidos en la comunidad que representan una fuente potencial de rreactivación o diseminación, de hecho, es mayor que en años anteriores.

c) Aunque la frercuencia de infección ha disminuído en los Estados Unidos, como se revela por las pruebas cutáneas de grupos selectos, se estima que hay todavía 50 a 60 milliones de reactores tuberculínicos que ofrecen una gran fuente potencial para la enfermedad endógena.

d) La tuberculosis es todavía el problema médico mayor en muchas otras partes del mundo, notablemente en Oriente, y, los Estados Unidos noestán completamente aislados de estas fuentes externas de infección.

e) La desatención de las medidas aceptadas de control, es de concebirse, podría resultar en un aumento de la frecuencia de la tuberculosis en este país.

2. En realidad, en el manejo médico quirúrgico del paciente individual con tuberculosis, el tratamiento es todavía de relativa larga duración sin haber un método rápido como para la lués.

a) Para una pequeña parte de pacientes con enfermedad extensiva,—quienes hubieran muerto hace algunos años, pero ahora son salvados por la—terrapéutica antimicrobiana, para permanecer como casos de custodia, hay todavía un definitivo problema de cronicidad.

b) Sin embargo, para la gran mayoría de pacientes, el tratamiento que abarca los antimicrobianos, la cirugía y los problemas previos de terapia de reposo los retorna a la vida activa en un período de tiempo más corto que en el pasado.

c) La tendencia creciente es a dudar de la importancia del reposo y de la necesidad de la cautelosa reanudación a las actividades normales.

d) Sólo la observación prolongada de los enfermos puede determinar la validez de esta nueva tendencia, pero las perspectivas de un rápido retorno a una existencia normal que resulta tan excitante para el paciente como para el médico, hacen que se imponga una prueba acuciosa del incremento en la ambulación temprana, especialmente en vista de la evidencia favorable que hay hasta ahora en este sentido.

RESUME

1. Malgré que le déclin marqué du taux de la mortalité tuberculeuse répand l'idée que cette affection a été jugulée dans le pays, la tuberculose présente encore un problème épidémiologique d'une ampleur considérable aux Etats-Unis.

a) Les statistiques de morbidité ne correspondent pas à la brusque chute du taux de mortalité tuberculeuse.

b) Avec les nouveaux cas observés, évoluant peu et les nombreux cas de malades que l'on peut sauver maintenant, alors qu'auparavant ils seraient morts, le nombre total de cas connus dans la collectivité qui gardent un potentiel de réactivation ou d'extension des lésions, est actuellement plus grand que dans les années passées.

c) Bien que la fréquence de l'infection ait diminué aux Etats-Unis, comme le prouvent les tests cutanés de groupements déterminés, on estime qu'il y a encore 50 ou 60 millions d'individus réagissant à la tuberculine, qui offrent un potentiel important de réinfection endogène.

d) La tuberculose est encore le problème de premier ordre dans beaucoup d'autres parties du monde, en Orient particulièrement, et les Etats-Unis ne sont pas complètement isolés de ces sources extérieures d'infection.

e) Le relâchement des mesures de contrôle pourrait vraisemblablement déterminer une augmentation de la fréquence de la tuberculose dans ce pays.

2. Dans le domaine de la thérapeutique médicale et chirurgicale de la tuberculose, le traitement est encore d'une durée relativement longue, sans moyen de traitement rapide, comme nous n avons maintnant contre la syphilis.

a) Pour un petit nombre de malades, atteints de lésions extensives, qui seraient morts dans les années passées, mais qui maintenant sont sauvés par la thérapeutique antimicrobienne, et qui restent à surveiller, il se pose encore le problème certain de la chronicité.

b) Cependant, pour la grande majorité des malades, le traitement par les médications antimicrobiennes, la chirurgie et la pratique déjà ancienne du repos, permet la reprise d'une vie active beaucoup plus rapidement.

c) La tendance actuelle est de rechercher la valeur que l'on doit attribuer au repos intégral et à la reprise prudente de l'activité dans la stabilisation et dans la prophylaxie de la rechute.

d) Ce n'est qu'en suivant pendant longtemps les malades que l'on pourra déterminer si la suppression de ces mesures est valable. Toutefois les perspectives d'un retour rapide à la vie normale provoquent un tel enthousiasme chez le malade et chez le médecin qu'une étude poussée sur la reprise précoce de l'activité apparait vraiment justifiée.

Teaching Chest Disease — Prevention*

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The maintenance of health is immeasurably more important than its restoration after disease has developed. Prevention of disease is the finest field of medical practice, and it is a serious question why it is only too often neglected by practicing physicians and relegated to public health workers, visiting nurses, teachers and, unfortunately, irregular practitioners, quacks and faddists.

Far too little is known and taught regarding specific measures which may contribute to the preservation of physical integrity, in particular, those relating to diseases of the chest. Yet, a wide variety of physical, chemical and biological measures is available for individual and social application in this field. A review of some of these measures may encourage more active teaching of this subject.

Noxious agents may sometimes be destroyed or inactivated on the outside or kept from gaining access to the body or invading the tissues. Even after they have entered the body they may be rendered harmless by killing, neutralization, encapsulation or expulsion by the physical, chemical or biological defenses of the host. Hostile agents which have entered the tissues or organs may fail to harm them or the lesion produced may be controlled even before it becomes demonstrable.

Geographic and meteorologic factors in the ecology of disease often seem beyond control but some precautions are available. Paving, planting or sprinkling may diminish outdoor dust and the danger of coccidiodomycosis. Sanitary engineering with the use of mechanical guards, wet processes, blowers, suction, air filters and the wearing of masks against industrial dust may avert pneumonoconiosis. The use of safety devices, especially safety belts and body armor, and personal vigilance and care to avoid hazardous exposures may allow escape from chest trauma in civilian and military operations. Community efforts to control domestic, industrial or vehicular atmospheric pollution by products of combustion, petroleum and its derivatives and other harmful substances and personal avoidance of excessive inhalation of cigarette smoke may lessen the danger of lung cancer in later years.

National and international governmental action may be necessary to eliminate the danger of direct exposure to radiation, or to contact, ingestion or inhalation of radioactive fallout following nuclear explosions but care in the planning and operation of dangerous sources of radiation and personal avoidance of sites of danger may diminish the risk. The therapeutic employment of radiation as in the treatment of breast tumors should be

*The eighth in a new series of articles prepared under the sponsorship of the Council of Undergraduate Education of the American College of Chest Physicians.

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carefully planned as to dosage, direction and shielding to lessen the danger of secondary pulmonary fibrosis.

The destruction of circumambient organisms by aerosols, as in Lister's carbolic acid spraying of operating rooms or in the ultra-violet irradiation of schoolrooms and other public places, is of limited value in the control of acute upper respiratory infection. Voluntary isolation or the use of masks during the infectious early stages of catarrhal conditions is hampered by the difficulty in early diagnosis, the generally low disability produced by the disease itself, and the dubious effectiveness of even the most wholehearted cooperation.

The effective treatment of upper respiratory conditions in order to prevent their giving rise to lower respiratory complications has been eloquently urged. Popular beliefs in the importance of adequate sleep or daytime rest, the avoidance of exhaustion or overwork, enthusiasm for exercise, fresh air, abundance of ventilation but avoidance of chilling and the recommendations for sunlight or ultraviolet irradiation, vitamins and other special nutrients and other measures for building up non-specific resistance against colds are, however, still to be verified, though that does not mean that they are necessarily baseless. Specific immunization or the prophylactic use of antibiotics against influenza and other acute upper respiratory infections in the general population are still controversial.

The prevention of allergies is still a mystery. The avoidance of pollens and other antigens or specific desensitization to the offending agent may lessen the precipitation of hayfever and some asthmatic attacks. Effective treatment post-operative atelectasis, of sinusitis and avoidance of post-nasal drip may lessen the incidence of later bronchiectasis. Keeping small objects out of the reach of infants and caution against placing objects in the mouth may lessen the danger of getting foreign bodies in air passages with consequent pulmonary suppuration.

Effective measures are available against a number of specific etiologic agents. Vaccination against whooping cough is now not only feasible but widely practiced. Diphtheria has been almost eradicated by the use of antitoxic immunization. The avoidance of exposure to psittacine birds, or perhaps the treatment of parakeets with a broad spectrum antibiotic to prevent their harboring the virus, may control the danger of psittacosis. Precautions against the vectors of rickettsial respiratory infections, such as scrub typhus, Q fever or Rocky Mountain spotted fever, may be taken if only the danger is recognized, and vaccines are available for those inevitably exposed. Avoiding wading in polluted oriental waters and thorough cooking of any product of such waters may prevent infestation with lung flukes.

The eradication of bovine infection by slaughtering of infected animals and the isolation of human cases of active tuberculosis have remarkably reduced tuberculous infection. Early diagnosis and the teaching and practice of personal precautions by patients and their contacts, with the sterilization of their excretions and fomites, offers even greater promise in the future. Vaccination with BCG or the administration of prophylactic chemo-

therapy with isoniazid may diminish the danger to negative tuberculin reactors who are heavily exposed to the tubercle bacillus under conditions where other precautions cannot be exercised. Chemotherapy for recent tuberculin converters or for cases of primary tuberculous infection in the lung, and especially patients with pleural effusion or minimal primary lesions, may prevent the development of more extensive disease.

An ideal regimen or way of life, with adequate nutrition, clothing, shelter, and mental hygiene of work, rest and recreation should protect from many of the pathological consequences of unhealthy living. Simple safety precautions are often sufficient to avert special dangers that can be foreseen. Sanitation of air, water, and food, and of the numerous contacts of daily life should lessen the dangers from physical, chemical and biological foes of man.

The examples cited above represent only a part of the steps that might be mentioned. Not only in formal courses in preventive medicine, but in almost every department of medical education, and in postgraduate training and everyday practice, advantage should be taken of every opportunity for learning and applying knowledge which may aid in the elimination of the causes of suffering, disability and death which have been the center of medical attention in the past.

Current trends indicate that the center of medical attention in the future will be on prevention for medical, social, and economic reasons. It is not too soon to include this interest in our teaching of chest disease.

FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

The Honorable Konrad Adenauer, Chancellor of The Federal Republic of Germany, has accepted an invitation to serve as the Honorary President of the Fourth International Congress on Diseases of the Chest to be held in Cologne, Germany, August 19 through 23, 1956, under the sponsorship of the Council on International Affairs of the College and with the cooperation of the Federal Republic of Germany and the City of Cologne. Professor Gerhard Domagk, discoverer of the sulfonamides and Nobel Prize Winner, is the President of this important World Congress.

The Cologne Cathedral overlooking the Rhine

The Committee on Scientific Program is now organizing the scientific program for the Congress, to include the most recent developments in pulmonary and cardiovascular diseases. Physicians having original work which they would like to present at the Congress are invited to communicate with Professor Andrew L. Banyai, Chairman, Council on International Affairs, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

The official languages of the Congress are German, French, Spanish and English and it is requested that abstracts of papers, in the language in which they are to be presented, as well as English translations, accompany all communications. Requests for places on the scientific program will be considered by the Committee on Scientific Program and authors whose papers are accepted will be notified promptly in order that there will be no delay in the preparation of their manuscripts.

The arrangements in Cologne are being supervised by the Executive Committee in Germany. Professor Joachim Hein, Schleswig-Holstein, Regent of the College for Germany, serves as Chairman of the Executive Committee. Other members are: Professor Ludwig Heilmeyer, Governor of the College for Freiburg; Professor Joseph Jacobi, Governor for Hamburg; Professor H. W. Knipping, Governor for Cologne; Professor Rudolf Schoen, Governor for Gottingen; Professor Walter Unverricht, Governor for West Berlin; Professor E. Wollheim, Governor for Wurzburg; Professor Hans Wurm, Governor for Wiesbaden; and Professor Rudolph Zenker, Governor for Marburg/Lahn (Hessen). Honorary members of the Committee are: Dr. Otto Buurman, Director, Department of Health, Ministry of the Interior; Professor Redeker, President of the German Central Committee Against Tuberculosis; Dr. Ernst Schwering, the Mayor of the City of Cologne; and Dr. Max Adenauer, City Director of Cologne. Additional members will be invited to serve with this Committee.

The International Travel Service, Palmer House, Chicago, Illinois, has been appointed the official travel agent for the Fourth International Congress. Information concerning pre- and post-convention tours may be obtained by writing direct to the agency.

AMERICAN AMBASSADOR TO SPAIN AWARDS COLLEGE CERTIFICATES

As an expression of appreciation for their cooperation in contributing to the success of the Third International Congress on Diseases of the Chest, held in Barcelona in October 1954, the American College of Chest Physicians awarded Certificates of Honor to His Excellency, the Chief of State, Generalissimo Franco, and to other Spanish Government and College officials.

At a ceremony held in the Embassy Residence in Madrid on May 20, 1955, Mr. John Davis Lodge, Ambassador of the United States to Spain, presented the certificates to Don Blás Pérez González, Minister of the Interior; Doctor José A. Palanca, Director General of Public Health and to the Marqués de Villaverde. The certificate for Generalissimo Franco was delivered to him at the Palace in El Pardo. In notifying the Executive Director of these presentations, Mr. Lodge stated:

> "From my experience as Governor of Connecticut and here in Spain as Ambassador, I have had ample opportunity to realize the immense amount of good these international meetings do towards making friendships that endure across national boundaries. For the good work the American College of Chest Physicians is doing for the betterment of the human race everywhere, my heartiest best wishes and congratulations."

Guests attending the presentation ceremony included various officials of the United States Embassy and relatives of those receiving certificates.

In a similar ceremony, held at the United States Consulate in Barcelona on June 3, Mr. Lodge presented Certificates of Honor to Don Martínez Borso, Chief of the Provincial Department of Public Health; Don Manuel Juamar de Bofarull, Chief of the Department of Public Health for the City of Barcelona;

Ambassador's Reception in Madrid

Left to right: The Marqués de Villaverde, Mrs. Nistal, who received the Certificate of Honor for her father, Dr. José Palanca, Director General of Public Health, Ambassador John Davis Lodge, Minister José de Cárcer of the Spanish Foreign Office who received the Certificate for Don Blás Pérez González, Minister of the Interior, and Dr. Nistal who was the Marqués' first teacher of thoracic surgery.

Doctor Luís Rosal, President of the Third International Congress on Diseases of the Chest and Governor for the College in Barcelona; and to Doctor Antonio Caralps, Secretary-General of the Congress. In addition, recognition was given to Don Felipe Acedo Colunga, Governor of Barcelona, Don L. M. Simarro, Mayor of Barcelona, the Marqués de Castell-Florita, President of the Barcelona Deputation and to Lt. General Don Bautista Sánchez González, Military Governor for the Fourth District of Spain. Guests attending the ceremony included Mr. Milton Wells, Consul General of the United States in Barcelona and officials from the American Embassy in Madrid.

The continuous growth of the College in Spain is evidenced by the fact that our 1952 College Directory listed 21 members while the names of 65 members are carried in the 1955 edition of the Directory which has recently been released. The Madrid and Barcelona Chapters were organized in 1953 and are actively engaged in promoting the scientific program of the College.

A two-day scientific meeting of the Madrid Chapter and our members in the Northern Provinces was held in Bilbao on June 16-18, 1955, under the direction of our Governor for Madrid, Doctor José Abello, who is also the Secretary of the Madrid Chapter, Doctor Carmelo Gil-Turner, Governor for the College in Bilbao and Doctor Alvaro Urgoiti, Governor for the College in La Coruña. Professor Antonio Crespo Alvarez of Madrid, Regent for the College in Spain, attended the meeting.

Two symposia were presented on June 16. Doctor J. Márquez and Doctors Luís L. Area and C. Otaduy of Bilbao composed the panel on "Constrictive Pericarditis" and Doctor José Abello of Madrid, Doctor Alvaro Urgoiti of La Coruña and Doctor Carmelo Gil-Turner of Bilbao participated in the symposium on "Bronchiectasis." Clinical sessions and case discussions were held on June 17 and 18 at the Grupo Sanatorial de Santa Marina.

At a business meeting following the scientific sessions, it was decided that a chapter of the College for the Northern Provinces of Spain would be formed, the organizational meeting to be held in La Coruña in December of this year.

Ambassador's Reception in Barcelona

Ambassador Lodge presenting Certificate of Honor to Professor Antonio Caralps, Secretary-General of the 3rd International Congress on Diseases of the Chest. *Left to right*: Ambassador Lodge, Don Felipe Acedo Colunga, Governor of Barcelona, Don L. M. Simarro, Mayor of Barcelona, Marqués de Castell Florite, President of the Barcelona Deputation and Doctor Luis Rosal, President of the 3rd International Congress.

The Barcelona Chapter of the College held a scientific meeting, attended by approximately one hundred physicians, at the University of Barcelona on June 11. A round table discussion on the "Prevention and Treatment of Postoperative Complications in Thoracic Surgery" was presented. The panel for this discussion consisted of Professors Ramón Arandes, Pedro Piulachs, Máximo Soriano and Doctors Antonio Caralps, Tomás Lorenzo, Felipe Margarit and Luis Trías de Bes. The President of the Chapter, Doctor José Cornudella, served as the moderator.

Those members of the College who attended the meetings in Spain in 1954 have fond recollections of the splendid hospitality extended to them by our Governor in Madrid, Doctor José Abello, and at the brilliant congress held in Barcelona under the Presidency of our Governor for Barcelona, Doctor Luis Rosal and the dynamic Secretary-General of the Congress, Doctor Antonio Caralps.

Because of their constant efforts in developing chapter activities, our officials in Spain are furthering the aim of the College by bringing recent advances in the treatment of diseases of the chest before the physicians of their country.

NEW COLLEGE OFFICIALS APPOINTED

Dr. James H. Stygall, Indianapolis, Indiana, President of the College, has announced the following appointments:

Dr. Arthur M. Olsen, Rochester, Minnesota, Regent of District No. 10, to complete the unexpired term of Dr. John F. Briggs, recently elected as Chairman of the Board of Regents.

Dr. Sumner S. Cohen, Oak Terrace, Governor of the College for the State of Minnesota, to serve the unexpired term of Dr. Arthur M. Olsen.

Dr. Howard S. Van Ordstrand, Cleveland, Governor of the College for the State of Ohio, to complete the unexpired term of Dr. David W. Heusinkveld, Cincinnati, deceased.

Dr. Alfred Kruger, Norfolk, Governor of the College for the State of Virginia, to complete the unexpired term of Dr. C. Lydon Harrell.

Brigadier General James P. Cooney, Deputy Surgeon General, U. S. Army, Washington, D. C., Governor of the College for the Department of the Army, to complete the unexpired term of Major General George E. Armstrong, retired.

Major General Dan C. Ogle, Surgeon General, U. S. Air Force, Washington, D. C., Governor of the College for the Department of the Air Force.

COMMITTEE ON MOTION PICTURES

Physicians who have recently prepared motion pictures on diseases of the chest (heart and/or lungs) are invited to send their films for review by the Committee on Motion Pictures of the College. Those approved will be listed in the directory of films now under preparation. Consideration is being given for films to be shown at the 22nd Annual Meeting of the American College of Chest Physicians, to be held in Chicago, Illinois, June 7-10, 1956.

A program of motion pictures is also planned for the Fourth International Congress on Diseases of the Chest which is to take place in Cologne, Germany, August 19-23, 1956, under the sponsorship of the Council on International Affairs of the College and the Federal Government of West Germany.

Film data forms will be forwarded upon request to physicians interested in presenting their films at the above meetings.

Please address films and inquiries to Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Other members of the committee are: Dr. Houck E. Bolton, Philadelphia; Dr. Alfred Goldman, Los Angeles; Dr. H. Corwin Hinshaw, San Francisco; Dr. David H. Waterman, Knoxville; and Dr. Francis M. Woods, Boston.

ANNUAL MEETING PROGRAM COMMITTEE

Dr. William A. Hudson, Detroit, Michigan, immediate past-president of the College, is Chairman of the Committee on Scientific Program for the 22nd Annual Meeting of the College to be held at the Sherman Hotel, Chicago, Illinois, June 7 through 10, 1956.

Physicians are invited to submit recommendations for the scientific program, as well as requests for places on the program, to Dr. William A. Hudson, Chairman, Committee on Scientific Program, David Whitney Building, Detroit 26, Michigan. Abstracts of scientific papers should accompany all requests for places on the program.

College Chapter News

INDIANA CHAPTER

The annual luncheon meeting of the Indiana Chapter will be held on October 18 at the French Lick Hotel, French Lick Springs. Following the luncheon, Dr. J. V. Sherwood, Fort Wayne, will speak on "Pulmonary Function Tests" and the meeting will be concluded with an x-ray conference.

MIDDLE EAST CHAPTER

Dr. Papken S. Mugrditchian, Beirut, Governor of the College for Lebanon, has announced that the Middle East Chapter, which includes Iraq, Jordan, Lebanon and Syria, will hold its first scientific conference at the Ambassador Hotel, Beirut, Lebanon, September 16-18.

NORTH CAROLINA CHAPTER

The North Carolina Chapter will meet at the Veterans Administration Hospital, Oteen, October 17. The scientific session and election of officers will take place in the afternoon, to be followed by a dinner at the hospital in conjunction with the Buncombe County Medical Society. Guest speaker will be Dr. Charles P. Bailey, Philadelphia, Pennsylvania, who has chosen the topic "Treatment of Trivalvular Rheumatic Heart Disease."

POTOMAC CHAPTER

The annual meeting of the Potomac Chapter will be held at the Greenbrier Hotel, White Sulphur Springs, West Virginia, on October 7. The following program has been arranged:

MORNING SESSION

"Morphological Changes in Tuberculosis"
M. L. Hobbs, Morgantown,, West Virginia
"Pulmonary Manifestations of Systemic Disease"
Harold S. Pettit, Charleston, South Carolina
"Mediastinal Tumors"
Edgar W. Davis, Washington, D. C.
Business meeting

12:00 noon Luncheon—Guest speaker, Charles E. Hodges, Managing Director, Charleston Chamber of Commerce, Carleston, West Virginia—
"West Virginia, Your Host, What Do You Know About It?"

AFTERNOON SESSION

"Medical Aspects of Cardiac Valvulotomy"
C. Edward Leach, Baltimore, Maryland
"Angiocardiography in the Diagnosis of Thoracic Disease"
Herbert Sloan, Ann Arbor, Michigan
"Preliminary Report on Cycloserine in the Treatment of Pulmonary Tuberculosis"
Ross L. McClean, Baltimore, Maryland
"Cancer of the Larynx"
Sobisca S. Hall, Clarksburg, West Virginia
"Diverticula of the Esophagus"
James H. Walker, Hopemont, West Virginia
"Biopsy of the Lungs and Pleura"
Otto C. Brantigan, Baltimore, Maryland
"Common Diseases Among Coal Miners"
Ralph Nestman, Charleston, West Virginia
Radiological Conference
Harold S. Pettit, Moderator

ROCKY MOUNTAIN CHAPTER

The Rocky Mountain Chapter will hold its annual meeting in the Spruce Room of the Shirley Savoy Hotel, Denver, Colorado, on September 24. Following is the program:

9:00 a.m. Registration
Unusual Malignancies of the Lung"
I. T. Lyon and Marvin Seife, Denver, Colorado
"Current Trends in the Chemotherapy of Tuberculosis"
Roger S. Mitchell, Denver, Colorado
"Common Errors in the Diagnosis of Pulmonary Disease"
Colonel James A. Wier, Denver, Colorado
"Mechanism of Experimental Auricular Flutter"
A. Lanari, A. Lambertini, A. Agrest, and A. Ravin
Denver, Colorado
12:00 noon Luncheon—Panel Discussion "Is Bed Rest No Longer Necessary in the Management of Pulmonary Tuberculosis?"
Sydney H. Dressler, Denver; Gardner H. Middlebrook, Denver; Roger S. Mitchell, Denver; Colonel James A. Wier, Denver; Jerome D. Textor, Wheat Ridge, and H. M. Van Der Schouw
Wheat Ridge
2:30 p.m. "Pitfalls in the Treatment of Pulmonary Emphysema with Carbon Dioxide Retention"
Henry Bradford, Denver, Colorado
"A Second Look at the Cardiac Patient"
Milton W. Anderson, Rochester, Minnesota

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter will be held at the Hotel Jefferson, Richmond, on October 16. The following program, commencing at 2 p.m., will be presented:

"Medical Aspects of Carcinoma of the Lung"
Dean B. Cole, Richmond, Virginia
"Fungus Diseases of the Lungs"
E. E. Menefee, Jr., Durham, North Carolina
"Modern Day Concept of the Treatment of Pulmonary Tuberculosis"
William A. Hudson, Detroit, Michigan
"Treatment of Childhood Tuberculosis"
Edwin L. Kendig, Jr., Richmond, Virginia
"Sarcoidosis—Modern Concepts"
Edward S. Ray, Richmond, Virginia
5:00 p.m. Business Meeting
7:00 p.m. Social Hour
7:30 p.m. Banquet. Guest speaker, Dr. William A. Hudson, Immediate Past-President, American College of Chest Physicians

College News Notes

Dr. Maurice S. Segal, Boston, Massachusetts, presented a series of lectures at the annual Postgraduate Medical Assembly of South Texas in Houston in July. Dr. Segal spoke on "Advances in Inhalational Therapy," "Advances in the Management of the Patient with Chronic Pulmonary Emphysema" and "The Present Status of ACTH and Cortisone in Diseases of the Chest." Dr. Segal also spoke before two medical groups in Mexico City. The meetings were arranged by Dr. Donato G. Alarcon, Regent of the College for Mexico, and Dr. Rocha. Dr. Segal also visited Dr. Rudolph Herrera of Guatemala City.

Dr. P. J. Sparer, Memphis, Tennessee, was recently elected President Elect of the Tennessee Psychiatric Association.

Dr. Aldo A. Luisada, Director of the Division of Cardiology, Chicago Medical School, has been awarded $25,000 by the National Institutes of Health as a teaching grant for cardiovascular diseases. Dr. Luisada and Dr. Harry J. Isaacs, Chairman of the Department of Medicine, have received $4,000 from the Chicago Heart Association for the research project "A Comparative Study of the Effects of Various Cardiac Glycosides in Heart Failure."

Dr. Edward Kupka, Berkeley, California, has returned from his assignment as Public Health Officer with the Foreign Operations Administration in Vietnam, Cambodia and Laos, to his position as Chief, Bureau of Tuberculosis Control, California State Department of Public Health.

The following members of the College presented papers in the scientific program of the Seventh Assembly of the American Academy of General Practice, held in Los Angeles recently: Charles A. Hufnagel, Washington, D. C.; Fay A. LeFevre, Cleveland, Ohio; Alton Ochsner, New Orleans, Louisiana; George Piness, Los Angeles, California.

Dr. Hawley H. Seiler, Tampa, Florida, was a guest speaker at the Sixth Mexican Congress on Tuberculosis and Silicosis held in Mexico City recently. Dr. Seiler presented papers on "Pulmonary Resection for Metastatic Malignancy" and "The Classification and Diagnosis of Mediastinal Tumors."

Dr. J. Frank W. Stewart, formerly Assistant Medical Director of Waverly Hills Sanatorium, Kentucky, has been appointed Superintendent and Medical Director of the Hillcrest Tuberculosis Hospital, Vincennes, Indiana.

Captain Edward R. Loftus, Chief of the chest disease clinic at the Fort McClellan (Alabama) Army Hospital was honored by the Army upon his release from active service with the Commendation Ribbon with Metal Pendant. Captain Loftus was cited for exhibiting initiative, organizational and administrative ability while serving as chief of his section. It was under his guidance that the chest disease clinic was organized. Dr. Loftus has resumed his civilian practice at the Veterans Administration Hospital, Manchester, New Hampshire.

Dr. Nathaniel E. Reich, Brooklyn, New York, has been appointed Consultant in Cardiology to the Long Beach Memorial Hospital and the Kings Highway Hospital.

Dr. Richard H. Overholt, Boston, Massachusetts, presented a paper on "Prophylaxis, Diagnosis and Treatment of Pulmonary Carcinoma" at the Primer Congreso Nacional de Medicos de Sociedades Regionales held in Havana, Cuba. Dr. Manuel Conde Lopez, Havana, a member of the College, officiated as President of the Congress, Dr. Antonio Navarrete, Havana, Regent of the College for Cuba, was Vice-Pres., and Dr. Luis Pascual, Havana, served as Secretary.

Dr. Louis L. Friedman, Birmingham, Alabama, has been appointed Coordinator of the Poliomyelitis Vaccine Program and Civil Defense Medical Coordinator for the state of Alabama.

Obituary

P. E. A. NYLANDER

1897 - 1955

On April 14, 1955, Finnish medical science suffered a heavy loss when Per Edvin Alfred Nylander, Professor of Surgery at the University of Helsinki, died suddenly of cardiac infarction while attending the congress of the German Surgical Association.

Born in Helsinki on December 11, 1897, Professor Nylander became a licenciate in medicine at the University of Helsinki in 1924 and received the degree of Doctor of Medicine in 1927. His thesis dealt with congenital fistulae and cysts of the neck. He was appointed docent in surgery at the University of Helsinki in 1930 at the age of thirty-three years, and became Associate Professor in 1940 and holder of the regular chair of surgery in 1943. Since 1944 he was, in succession, Director of the Second and First Surgical University Clinics. Professor Nylander completed his medical studies by making several visits to other countries, during which he attended a number of conferences. Among the countries he visited, in addition to the other Scandinavian countries, were Germany, Great Britain, Italy and finally, in 1948, the United States. He attended the First International Congress on Diseases of the Chest in Rome (1950) and the Third International Congress in Barcelona (1954).

While a university docent, Professor Nylander was particularly attracted to problems in thoracic surgery. This was the field in which his achievements were the greatest. It was Professor Nylander who introduced modern thoracic surgery, particularly pulmonary resection and operative treatment of the heart, into the country. He was a pioneer in this field. Professor Nylander edited DUODECIM from 1936 to 1940. He was editor of ANNALES CHIRURGIAE ET GYNAECOLOGIAE FENNIAE since 1945; and was on the editorial panel of the surgical section of EXCERPTA MEDICA.

Professor Nylander was a member of the Finnish Surgical Association (President 1944-1947), Societe Internationale de Chirurgie, Deutsche Gesellschaft für Chirurgie, Nordisk Kururgisk Förening, Svenska Läkaresällskapet, et norske medicinske Selskab, and the Societe Europeenne de Chirurgie Cardio-vasculaire (delegué). He was a Fellow of the American College of Chest Physicians and served as Governor of the College for Finland and as first President of the Finnish Chapter.

Professor Nylander was married to Rakel Pohto in 1928. They have four children, three sons and a daughter.

Professor Nylander's career was characterized by devotion to his calling. An excellent surgeon and teacher, he holds a distinguished place in the annals of Finnish medicine. Besides, he was a man of strong but warm personality and there are many who mourn the loss of a good, loyal friend.

Jorma Pätiälä
Secretary, Finnish Chapter

BOOK REVIEWS

OMPHALOSOPHY AND WORSE VERSE. By William B. Bean, M.D., University Hospital, Iowa City, Iowa.

One of this country's diminishing band of medical versifiers has collected into a booklet sundry items of his stray and errant verse. This is chiefly, but not entirely, medical. The main item is a long discourse on the navel under the pleasant title of Omphalosophy in which the gentle barbs of irony are employed in poking fun at some aspects of the contemporary scene, both medical and general. Every physician with a sense of humor and the desire to "see ourselves as others see us" should obtain a copy of this collection which is rapidly achieving the status of a minor league classic. Copies of this collection are still obtainable from the author for the modest price of fifty cents. It is highly recommended to physicians everywhere who enjoy an evening or more of wholesome entertainment. Caution. Apply binder and keep well fastened while reading this pamphlet.

J. Arthur Myers, M.D.

AN INVESTIGATION OF EMOTIONAL AND SOCIAL CONCOMITANTS IN THE IRREGULAR DISCHARGE RATES OF HOSPITALIZED PATIENTS WITH TUBERCULOSIS: A Doctor's Dissertation, University of Pittsburgh, 1954. By Edward William Speth, B.S., M.S.

This monograph is a psychological research study of irregular discharge among tuberculous patients undertaken by E. W. Speth in partial fulfillment of his Ph.D. degree at the University of Pittsburgh. The psychological reactions of tuberculous patients to life situations were investigated by means of their performance on psychological tests and questionnaires in an attempt to find some general characteristics which may suggest psychological components basic to irregular discharge.

Data were collected for a specified time on incoming tuberculous patients of the VA Hospital in Butler, Pennsylvania and all the patients were given at least six months to react to the stress of hospitalization. The Minnesota Multiphasic Personality Inventory (MMPI) was used as a quantitative measure of personality in nine areas expressed by certain clinical scales. In this connection it should be noted that rather than measuring pure personality traits or representing discrete etiological or prognostic entities, the MMPI was designed to provide an estimate of syndromes commonly recognized among persons with clinical problems; and the mere presence of deviant personality factors does not necessarily imply that the person is physically or mentally handicapped since an understanding of the personality functions would require a complete configuration of the personality.

Dr. Speth properly recognizes the special need for adequate mental conditioning of the patients and for applying the personal touch in the relationship between patient and attending personnel. He calls attention to the importance of considering the patient's source of his difficulty resulting in irregular discharge. And he indicates that the literature on tuberculosis defines two chief sources; one concerns the psychic factors present in the etiology of tuberculosis, the other concerns psychic factors which develop in the individual because he has tuberculosis; and these factors refer to general components which may be present in all tuberculous patients. However, Dr. Speth reasons that since all tuberculous patients do not leave institutions against medical advice it would seem that some other emotional factor might be responsible for this action, such as the factor or factors concerned with the individual's characteristic reaction to stress, his ability to tolerate pressures, the resources he is able to call into play, the defenses he has utilized to remove himself from trying situations, together with the amount of emphasis he places on the emotional concomitants which may be associated with tuberculosis; and it is this group of factors which invite investigation.

The author presents an excellent pertinent survey of the literature and an up-to-date chronological bibliography. In relation to the personality attributes of the tuberculous patient, the author points out that there has been little scientific investigation. He states that not only are the themes recurrent and contradictory but there is no agreement that the observed differences are the

result of the disease, predisposing factors to the disease, or merely accentuations of the stress of the illness; and the theories range from a mere description of the personality attributes of the tuberculous to conclusion of concomitant neuropsychiatric components.

On the basis of significant findings, Dr. Speth considers that the following assumptions, among others, appear tenable:

1. Tuberculous patients deviate in the direction of maladjustment on each of the nine personality scales of the MMPI.
2. All tuberculous patients recently admitted to the hospital have high depression scores; those new admissions with previous hospitalization having the highest scores. Depression as manifested on the scale of the MMPI shows some decrease with patients who are able to adapt and maintain hospitalization.
3. Irregular discharge has a direct relationship with the scales of psychopathic-deviate, hypochondriasis, and hysteria. However, hypochondriasis and hysteria have some significant relationship to repeated hospitalization. This leaves psychopathic-deviate as the only scale directly related to irregular discharge.
4. The frequency of irregular discharge, in general, appears to be directly related to the elevation of the score of psychopathic-deviate.
5. The lower educational status of the patient with irregular discharge appears to have some relationship to his inability to establish emotional rapport and suggests that the conflict and dissatisfaction he experiences is of a general rather than a specific nature.
6. The military status of tuberculosis, which appears as one of the most significant aspects of the study for identifying the irregular discharge patients, is open to question. Although the nonservice-connected veteran appears better able to maintain hospitalization than one with service-connection for tuberculosis, the preferential treatment regarding hospitalization accorded the service-connected veteran may be producing an artifact here. With hospitalization withheld from him over a period of time, it may be that the nonservice-connected veteran is a new admission who has not had the opportunity for irregular discharge and repeated hospitalization.
7. The factors of age, race, intelligence, marital status, and number of dependents have a negligible effect upon the discharge status of tuberculous patients.

The author concludes that all incoming tuberculous patients showed depression, patients with previous hospitalization showing the most depression. Along with depression, hypochondriasis and hysteria are the other psychological concomitants of stress which make up the neurotic triad in these patients and appear to be directly related to irregular discharge and rehospitalization. The only personality scale which appears to be singularly concerned with irregular discharge is that of psychopathic-deviate, the higher the score on this scale the greater the possibilities of irregular discharge occurring and being subsequently repeated. Dr. Speth mentions that no attempt was made to discount or deny the presence of situational variables within the hospital, such as fear of surgery or other recommended procedures, or the many inducements outside the hospital which bring pressure to bear upon the patient's ability to withstand the stress of hospitalization.

The author's thesis combines understanding, skill and scholarship at the graduate student's level and leads to a better appreciation of the psychological aspects of irregular discharge among tuberculous patients. Rather than offering a complete psychological answer to the irregular discharge problems, the results of the study have only suggested a psychological patterning, reflected in part by some social variables, which might be useful in predicting, and perhaps reducing if not preventing, the occurrence of irregular discharge.

P. J. Sparer, M.D.

ANNOUNCEMENTS

Lakeside Laboratories of Milwaukee, Wisconsin, announces a new bronchodilator drug that may provide an oral, safe means of preventing attacks of asthma as well as relieving them. Dr. Hollis G. Boren of Houston said the drug was effective orally in improving ventilation in various respiratory conditions and was apparently free from significant side effects even after prolonged maintenance dosage. Palpitation and tachycardia are effects often associated with the use of other bronchodilators, many of which are sprayed or injected. "Striking improvement" was demonstrated in some cases even though the patients had previously failed to respond to a full therapeutic program, Dr. Boren said. Dr. Boren is the first physician to report on clinical tests of the new bronchodilator, synthesized by Lakeside Laboratories, Inc. and known as JB-251, which is N-(2-(3,4 methylenedioxyphenylisopropyl) norepinephrine hydrochloride.

Parke, Davis and Company of Detroit, Michigan, has announced a new antibiotic preparation, combining two drugs, Chloromycetin and dihydrostreptomycin, for the treatment of various enteritic infections. Called Chlorostrep, the new preparation has been successful in treating susceptible infections of the diarrheal type, and mixed infections encountered in bowel surgery. Wide laboratory and clinical testing has proved that Chlorostrep is more effective in many instances than is either drug alone, the company said.

A team of two medical investigators reported on the use of Chlorostrep in a 30 year old patient with pulmonary tuberculosis, active sacroiliac and sacral tuberculosis and a tuberculous rectal fistula. Therapy was instituted on a dosage schedule providing 250 mg. of each antibiotic every six hours. The rectal fistula closed completely without drainage after 27 hospital days, although chemotherapy was continued for a total of eight weeks after admission. The antibiotic combination was employed also in patients with chronic anal fistula of the horseshoe variety, in which healing appeared to be definitely facilitated.

A revolutionary new type of elastic pressure bandage has been developed by Connecticut Bandage Mills, Inc., Bridgeport, Connecticut, called Elastafoam. It combines a purified foam rubber mass vulcanized to a cotton elastic bandage with longitudinal slits to permit a non-narrowing bandage and also to enhance the breathing ability of the foam. Post-operatively, it is used either with or without gauze dressings by making one lap around the patient and clipping the bandage in place. No adhesive is used and no record of secondary dermatitis has been found. Elastafoam is most effective as an impregnated or plain pressure burn dressing. Also used in fracture traction and other orthopedic work, is absorbent and non-toxic, and can be impregnated with medicinals after sterilization.

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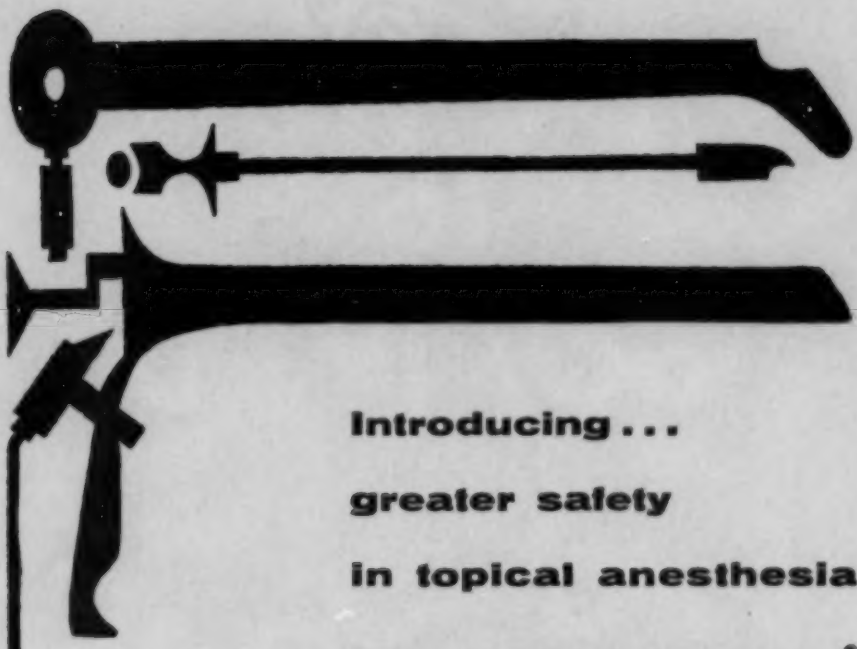

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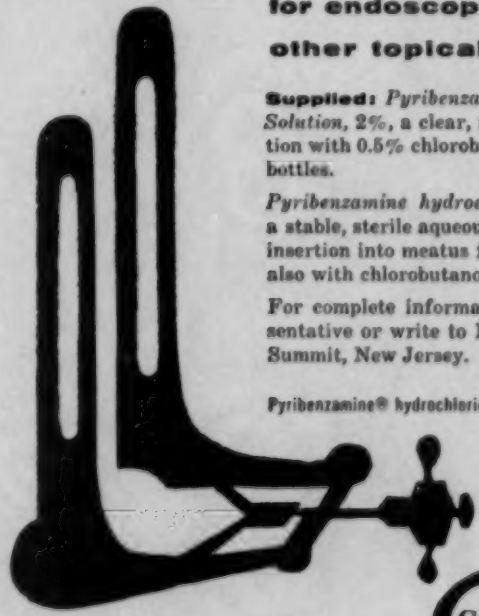

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References:

(1) *V.A. Quarterly Prog. Report, April '53 Bronx VA Hosp., N Y.*

(2) *V.A. Quarterly Prog Report, Oct. '54 Rutland Heights VA Hosp., Mass.*

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